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THE FRANK E. BUNTS INSTITUTE

will present

A Course In

Benign and Malignant Tumors

on

MONDAY, TUESDAY, and WEDNESDAY
APRIL 3, 4, and 5, 1939

A description of the course and an outline of the subjects to be covered will be found on pages 163-165.

HEPATICODUODENOSTOMY

Report of a Case

T. E. JONES, M. D.

This case is presented as one which is rather typical of an injury to the common duct during cholecystectomy. Anomalies of the duct account for a few accidents, but the majority result from incomplete exposure of the duct during operation or clamping blindly for hemorrhage in cases where the cystic artery slips away from the clamp or the ligature becomes loose. The cystic artery is a branch of the right hepatic and comes off at a level above the cystic duct so that in our cases the damage has invariably been in the hepatic duct at a distance of one-fourth to one inch below the bifurcation of the right and left hepatic duct.

The diagrammatic sketch shown in figure 1 shows also that the right hepatic artery may be clamped and tied off if the hemostats are put on blindly, leading to damage to the right lobe of the liver. In the case reported here, the physician stated that the gallbladder was acutely inflamed and, during the operation, he encountered severe hemorrhage which necessitated the blind application of the hemostat. This can easily

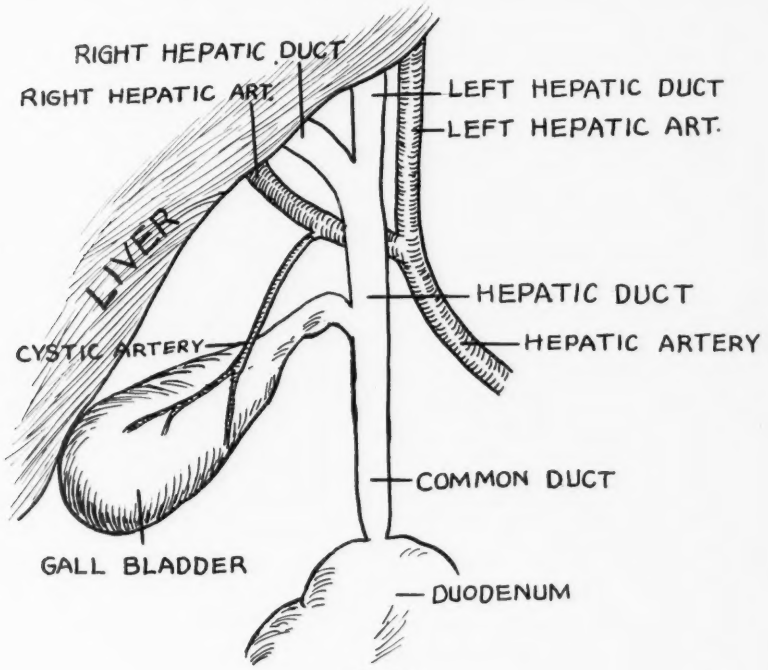

FIGURE 1

be avoided, however, if one places the finger in the foramen of Winslow and compresses the gastric hepatic omentum, through which the main vessels run, between the thumb and forefinger. Then on gradual release of pressure, the one bleeding point may be picked up and drainage to the duct obviated.

I have now performed hepatico- or choledocho-duodenostomies in 10 cases. Most of these were necessary because of injury during cholecystectomy which had not been recognized at the time. At the time of the secondary operation, the lower end of the common duct cannot be recognized in the majority of these cases and in those cases where it is recognized, the distance between the cut ends is frequently too great for anastomosis. Furthermore, in cases where it is possible to anastomose the cut ends, experience has taught us that the likelihood of reformation of the stricture is very great, necessitating further surgery; therefore, it has been our experience that anastomosis to the duodenum gives a much better end result.

Case Report

A man, 32 years of age, was admitted to the Clinic on January 4, 1939, complaining of jaundice and generalized pruritus. Ten months previously, in March, 1938, cholecystectomy for cholelithiasis had been performed elsewhere. The presenting symptom at that time was pain which had been present for three days in the upper part of the abdomen. Jaundice had not been associated with this symptom. The immediate postoperative course had been stormy; jaundice developed and on the fourth day the incision broke down and bile drained from it. However, this had healed within three weeks and the patient was able to leave the hospital.

Mild jaundice without pain persisted with varying intensity until six weeks before entrance to the Clinic when it became more pronounced and was associated with generalized itching. At no time had there been abdominal pain. Stools had varied from yellow to clay in color and the urine had been dark. The past history was negative except that thyroidectomy had been performed for diffuse goiter with hyperthyroidism in July, 1936.

Physical examination revealed a frail young adult who weighed 126 pounds. The temperature was 97.9° F., the pulse rate 80, and respirations 20. The skin presented a moderate icterus and the sclerae were slightly tinged. Recent excoriations due to pruritus were scattered over the trunk and extremities.

Examination of the abdomen revealed the liver to extend one finger's breadth below the costal margin. No other masses and no tenderness was detected.

On admission, a diagnosis of stricture of the common duct was made.

Blood studies revealed 4,640,000 red blood cells with 87 per cent hemoglobin, 11,500 white cells with 62 per cent polymorphonuclears, and an icterus index of 20 units. The prothrombin time was determined and found to be 15 seconds, 20 seconds being normal.

Twenty cc. of a 10 per cent solution of calcium gluconate, together with 1000 cc. of a 5 per cent solution of glucose in saline was given intravenously each day for five days, affording marked relief from the pruritus. Repeat studies of the blood on the fifth day showed that the icterus index had risen to 25 units while the prothrombin time was 17 seconds.

An exploratory laparotomy was performed January 10, 1939. Hugging the under surface of the liver, adhesions were divided, finally exposing the portion of the hepatic duct about 1 cm. from the liver (Fig. 2A). A probe was passed into the duct which was lightly dilated, liberating a considerable quantity of normal appearing bile. The probe could then be passed easily into the right and left hepatic ducts, the openings of which could be visualized through the end of the hepatic duct. However, on attempting to explore in the downward direction toward the common duct, obstruction was encountered and the common duct could not be demonstrated. The duodenum was mobilized and brought up to approximately the end of the previously dissected common hepatic duct. An opening was made into the duodenum and an anastomosis with the stump of the duct was constructed over the limbs of a T-tube. It was necessary to place one limb in the left hepatic duct in order to make it stay in place (Fig. 2B). It was noted that bile flowed from the long end of the tube and that none escaped at the site of the anastomosis. A transfusion of 500 cc. of citrated blood was given during the operation.

On the second postoperative day the T-tube was clamped off for two hour intervals without causing discomfort or leakage of bile around the

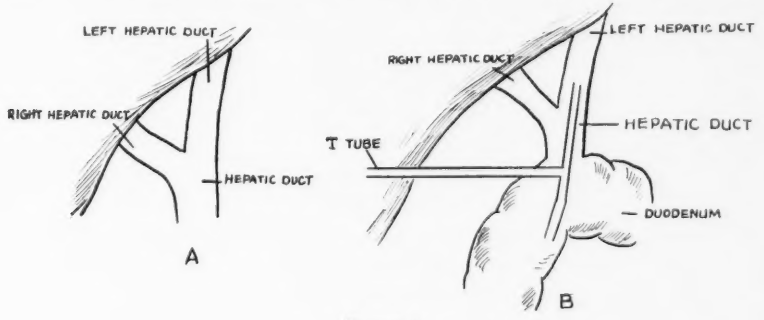

FIGURE 2

tube. The following day the clamp was applied continuously without untoward results.

By the sixth day the stools were dark in color and it was apparent that bile was passing into the intestines but the icterus index remained at 20 units. The prothrombin time remained normal and there was no indication of a hemorrhagic tendency.

On the sixteenth day the icterus index had fallen to 10 units and the jaundice had obviously decreased. At the time of discharge on the eighteenth day (January 28, 1939) the patient looked and felt greatly improved, the stools were dark in color, and the tube had remained clamped off without leakage for several days.

When examined twelve days later (February 9, 1939) the patient weighed 133 pounds, a gain of 7 pounds, and the icterus index was 10 units. His appetite was excellent and he felt excellent.

THE INVESTIGATION AND PROLONGED CARE OF THE ALLERGIC PATIENT

J. Warrick Thomas, M. D.

It is only by a careful and detailed study of the patient with allergy that a satisfactory solution of his problem may be reached and an effective program outlined for his future comfort. The chief complaint often gives the first indication that a patient has allergy, but this single factor should not in any way influence the detail with which a history is elicited.

History

Regardless of the chief complaint, all previous illnesses should be reviewed briefly according to the systems involved and careful inquiry should be made regarding anything that might have a bearing on the present complaint.

This review of the systems begins with the eye, ear, nose, and throat, an endeavor being made to elicit any previous involvement whether of infectious, traumatic, or congenital origin. Any and all operations on the nose or throat with their definite dates, the reason for operation, and the result should be listed. The review of the respiratory system will frequently overlap that of the ear, nose, and throat, but this is an advantage as certain facts may be emphasized that otherwise might be overlooked. Careful questioning may reveal details that have a bearing on the patient's allergy such as frequent infections of the upper respiratory tract in childhood, bronchitis associated with wheezing or unusual or abnormal respiration. The cardiovascular system is important from the standpoint of cardiac asthma in contrast to bronchial asthma. The dizziness or pounding in the head of the hypertensive individual must be contrasted with symptoms of migraine; attacks of anginal pain associated with other cardiac manifestations must be differentiated from precordial pain. Attacks of urticaria and gastro-intestinal discomfort must be carefully evaluated in regard to their etiology.

The history prior to the time of the present illness may reveal recurrent attacks of abdominal cramps, diarrhea, or vomiting that may be attributed to some food or be of unknown cause. Conditions such as peptic ulcer, gallbladder disease, various types of colitis or amebiasis must be differentiated from those of gastro-intestinal allergy. The occurrence of various rashes on the skin may be related to the diet or contact. Pain in the region of the bladder or difficult or painful urination as well as kidney colic may be referable to allergy. Certain joints at times may have caused discomfort, characterized by hydrarthrosis, pain, etc. Any attacks of angioneurotic edema involving the arms, wrists, or feet, as well as the face, should be noted in the history. Any operative pro-

cedures that may have a bearing on the case should be discussed thoroughly.

In both the male and female it is well to consider the marital history, especially the health of the husband or wife, as the case may be. It is important to know whether the patient was one of twins. Miscarriages and the health of the children living as well as the cause of death of any others is important.

In children, especially, an accurate history of infectious exanthemata, whooping cough, measles, vaccinations and innoculations, injection of serums, mastoiditis, otitis media, and vaginal discharge should be elicited.

Careful attention should be given to the chief complaint. The time of onset of the first symptoms as well as the duration of the attacks are important. The recurrence of attacks, whether seasonal or perennial, and the influence of climate must be considered, as the presence of these factors may have a definite bearing in certain cases.

Environmental contacts are also important. There should be an accurate description of the construction of the house in which the patient lives, when it was built, when the patient first moved into it, and the length of time he has lived there. A knowledge of the neighborhood may be of importance. He should be asked whether there are other cases such as his in the locality and what trees, plants, flowers, fields, weeds, insects, factories, smoke, and odors prevail in his environment. The heating system of the house is of the utmost importance as certain types may precipitate or aggravate many of the manifestations of allergy. The presence of dust and methods of cleaning may explain the recurrences or the precipitation of an attack, as well as its aggravation. Certain rooms or pieces of furniture may be suspected as causing trouble. The presence of dampness in certain parts of the house should have due consideration if they have a bearing on the case. Pets and even rats or mice have all been found to precipitate trouble. Flowers in the home have repeatedly made some patients miserable. The patient's bedroom is especially important; inquiry should be made regarding the occurrence of attacks there, in other parts of the house, or away from home. Other questions regarding his environment are: Does he sleep alone or room alone ? Have pillows or mattresses been covered, and what kind of floor or wall covering does the room have? Are there curtains in the room? Are pets frequently in the bedroom or are plants and flowers present?

Careful consideration should be given to the patient's occupation—contacts, ventilation, dust, flowers, business relations, etc.; any one of these factors may be of the utmost importance.

The effect of temperature, whether indoors or outdoors, as related to the symptoms is of significance. Inquiry should be made regarding bathing habits, including the time and temperature of the bath and the kind of soap used. Nervous factors and contact with other persons are also of importance.

Physical Examination

The physical examination of the allergic individual requires a more detailed investigation than the routine physical examination. The following points should be stressed:

Under the "status praesens," the following should be noted:

Apparent age
Hypersthenic
Sthenic
Normal
Hyposthenic
Asthenic
Obese
Thin
Emaciated
Robust
Anemic
Frame
Musculature
Temperature
Height
Weight
Normal weight of individual

Examination of the skin should include observation of:

Scalp: seborrhea
Hair: color, texture, amount
Beard: body hair
Nails and skin
Color, temperature, and moisture of axilla, palms and soles
Elasticity of skin and eruptions in addition to scaling, pigmentation, scars, vaccination scars, ulcers, and tumors.

In the ophthalmologic examination, the state of the following should be noted:

Lids, sclerae, conjunctivas, corneas, irises, and lacrimation.

In the examination of the respiratory system, one should note any nasal obstruction, septal defects, abnormality of the turbinates, amount of anterior or posterior nasal discharge, and tenderness over the sinuses.

The size and appearance of the tonsillar pillars should be recorded.

In the examination of the thorax, its contour and the type of respirations should be studied as well as other physical findings in the lung.

The more important points in the enterologic examination to be stressed are:

Herpes
Ulceration and fissures of the lips
Ulceration, exudation, and pigmentation of the mouth as well as the odor of the breath
Ulceration, fissures or areas of pruritus around the anus.

The genitalia should be examined to determine the presence of edema or pruritus.

Tests for Allergy

When the history and physical examination have been completed, the allergic investigation should be instituted. Routine laboratory examinations should always be carried out as well as any special tests that may appear desirable such as gallbladder drainage, various cultures, roentgen studies of the sinuses, chest, or gastro-intestinal tract.

The following tests for allergy are to be considered:

Cutaneous: inhalants and ingestants; endermal inhalants; endermal ingestants; seafoods (cutaneous and endermal); trees, weeds, and grasses; oidiomycin and trichophytin; stock molds and yeast.

Intracutaneous bacteria

Mantoux

Patch tests with clothes, soaps, orris root, ursal, pyrethrum, feathers, and other materials.

Passive transfer tests

Autogenous dust

Autogenous molds

Ophthalmoscopic studies

Nasal smears

Examination of the sputum, differential count and bacterial identification: cultures of sputum for bacteria and molds, etc.

Autogenous rhinopathogen and enteropathogen vaccines

Pure culture vaccines

Leukopenic indices

Special studies or tests

Consultations with other departments or specialties is of the utmost importance in some cases.

When all the investigations have been completed, the data are correlated and the program of treatment outlined. Many factors govern the regimen that is to be instituted. In cases of simple seasonal hay fever, the therapy to be used is influenced by the time of year the patient is first seen, i.e., just before the season, during the season, or after the season. Some patients are placed on a preseasonal regimen only, others are given perennial therapy, while still others receive coseasonal treatment if they are seen first during the pollen season. When success has not followed desensitization of the patient by the preseasonal or perennial method, a combination of these with the coseasonal program of treatment is used.

In cases of perennial rhinitis and asthma due to the common inhalants, the therapy consists of the avoidance of the allergens causing the trouble as well as desensitization. When there are multiple etiological factors

to be considered such as foods, common inhalants, and pollens, the relative importance of each must be evaluated carefully and suitable therapy outlined.

Patients who have atopic dermatitis alone are usually placed on diets eliminating the foods known to cause their trouble as well as foods that have given positive reactions by the skin tests or leukopenic tests. Some of these individuals fail to improve on such a program and then it becomes necessary to consider the keeping of a food diary by which a correlation may be made between the symptoms and the foods eaten. Elimination diets are found to be of value in some cases. When additional manifestations of allergy are present, these must be treated in conjunction with the atopic dermatitis before improvement is noted.

For patients with migraine, a regimen is prescribed for the elimination of foods that are known or suspected of causing trouble. In this group of individuals the food diary has proved valuable by showing that additional foods should be eliminated from the diet. In certain cases of migraine, it is necessary to treat other allergic manifestations before definite improvement occurs.

In the group of individuals who have gastro-intestinal allergy, it is well at the beginning of treatment to eliminate not only the foods known or suspected to cause trouble but, in addition, to remove any laxatives or cathartics whose contents are unknown. Some of these contain phenolphthalein or other ingredients that may produce definite symptoms, as evidenced by improvement following their removal. The food diary here again has been found to be an important adjuvant in detecting foods that would not be suspected otherwise. The food diary may falsely incriminate certain foods, but this is overcome by eliminating the entire group of suspected foods for a period of time. One at a time, the foods are restored to the diet, that food being ingested one or more times each day for a period of five days. If no symptoms occur at the end of this period, the food may be retained in the diet permanently. If the food is found to cause definite symptoms, it should be eliminated from the diet indefinitely.

In outlining the program of individuals sensitive to the common inhalants such as dust, feathers, orris root, pyrethrum, tobacco, smoke, silk, kapok, etc., careful instructions should be given regarding their avoidance and elimination. In the case of orris root, cosmetics that are hypo-allergic should be recommended and the patient should be familiarized with different preparations that are frequently found to contain orris root. Written instructions for the avoidance of dust and the preparation of a dust-free room should be given to patients.

In most of the cases referred to the Allergy Department of the Clinic the referring doctor is sent a complete report of the investigation undertaken. This report consists of a brief history dealing with the allergic manifestations that were found; the physical examination is reported in regard to the findings having a bearing on the allergy; laboratory studies are briefly outlined and any abnormal findings are elaborated upon; the results of the allergy tests that give positive reactions are outlined, and appropriate therapy is suggested. In addition, copies of the skin tests are inclosed. Not only is the immediate program outlined but consideration is given to any therapy that may be incorporated later.

Summary and Conclusions

This paper has been presented to emphasize the importance of a detailed study of each allergic patient in regard to history, physical examination, and the outlining of the program of investigation. The data obtained from such an investigation are correlated with the other findings and an appropriate program of treatment is outlined. The referring doctor is sent a complete report with copies of the various tests, together with instructions for the care and treatment of the patient. Patients are requested to report their condition directly or through their physician for a period of at least one year, that is, through the four seasons, in order that the program of treatment may be modified from time to time as necessary.

SUMMARY OF SOME LABORATORY METHODS IN ENDOCRINOLOGY

D. Roy McCullagh, Ph.D. and Ross Guillet

In the diagnosis and treatment of endocrinological disorders, the clinician has had the assistance of the clinical laboratory for a number of years. For example, disorders of the parathyroid glands involve calcium metabolism, and diabetic conditions alter the level of blood and urinary glucose. All well-equipped hospital laboratories are prepared to investigate these problems. Certain studies, however, involve specialized technics which are not usually available to the physician who is faced with an endocrinological problem. Although these technics are specialized, they are not difficult and any of them can be mastered by the average technician. In this paper we summarize the methods employed at present in the endocrine laboratories of this institution. These laboratories are part of the clinical division of endocrinology which is under the direction of Dr. E. Perry McCullagh. The methods have been adapted or devised in the Research Division of the Cleveland Clinic Foundation. A considerable portion of this work was done in collaboration with Mr. W. Kenneth Cuyler who was particularly interested in studies relating to the endocrinology of the female.

Determination of Androgens in Urine

Several chemical methods[1,2,3] have been described for the determination of androgenic steroids. In our hands, none of these has been completely satisfactory. We therefore continue to use biological methods of assay.

The method is as follows: A 24 hour specimen of urine is collected without preservative. The urine is acidified, using 50 cc. of concentrated hydrochloric acid per liter, and hydrolyzed for 15 minutes by boiling over a free flame. It is then extracted by stirring violently for ½ hour with dibutyl ether, using 200 cc. of solvent per liter of urine. The ether is separated from the urine by decantation and the use of a separatory funnel. There is usually very little emulsification but any emulsion which exists is placed in a separatory funnel along with 15 cc. of a 10 per cent solution of sodium taurocholate. When this is thoroughly mixed, the emulsion breaks down and the solvent is separated carefully from the aqueous phase, being sure that the precipitate of taurocholate does not contaminate the dibutyl ether. A second extraction is done in the same manner and the combined extracts are washed twice with 25 per cent by volume of a saturated solution of sodium bicarbonate, and twice with warm tap water. The dibutyl ether is then evaporated to dryness by steam distillation in partial vacuum.

This is accomplished as is the usual vacuum distillation except that, instead of admitting small quantities of air into the distilling flask, steam is admitted from a source which has an independent vent into the sink. The amount of steam admitted is controlled by a small stopcock or thumbscrew. To assure complete dryness, the steam is shut off for a few minutes at the completion of the distillation. The residue is removed from the flask to a beaker using ethyl ether; 25 cc. of oil are added and the ether removed on a water bath.

The amount of hormone in the oil is determined by a method, the principles of which are based on the work of Gallagher and Koch[4]. One cc. of oil is injected into the pectoral muscles of each of five white leghorn capons daily for five days. On the sixth day the comb is measured and the size compared to the size before treatment. The growth is expressed as the increase in length plus increase in the height of the comb as measured in millimeters. Birds with small combs show less growth than birds with large combs. The average comb length is 57 mm. and the comb growth of all birds is corrected accordingly. The correction factor is 0.17 mm. If the original comb length is less than 57 mm., 0.17 mm. of growth is added for each millimeter of difference between 57 and the original comb length. If the comb is greater than 57 mm., a similar correction is made in the opposite direction.

The amount of androgenic material being excreted is expressed in terms of androsterone. The equation for calculation is $y^2 = .43x - 3$ where y is the growth of the capon's comb in millimeters (length plus height) and x is the amount of androsterone injected per bird per day. External conditions influence the response of the capon's comb to androsterone and if great accuracy is required, a group of control birds should be injected. Normally 0.1 milligram of androsterone (1 international unit) daily will cause a growth of 6.6 mm. If the control group varies from this, the comb growth of the birds used in the assay is corrected accordingly. Further details concerning the response of the capon's comb to androsterone can be found in a paper by McCullagh and Cuyler[5].

If capons are not available it is possible to use the growth of the chick's comb as a method of assay[6]. Statistical studies concerning the use of chicks will be published from this laboratory in the near future.

Normal individuals excrete from 20 to 100 international units daily. Pituitary, testicular, and adrenal pathology may alter this output.

Assay of Androgens in Blood

Androgens may be measured in blood by the method of McCullagh and Osborn[7]. Thirty cc. of oxalated blood are laked with 270 cc.

of water and 15 cc. of concentrated sulfuric acid. This mixture is then hydrolyzed, extracted, and concentrated in the same manner as described for urine and is finally taken up in 5 cc. of sesame oil. The amount of hormone present is too small to permit of assay by the methods described above. It is possible to determine the amount of hormone in the oil by means of inunction methods[5]. Frank, Klempner and Hollander[8] describe a method of assay using the chick. The capon technic is briefly as follows: The comb of each bird is inuncted daily for 5 days with 0.2 cc. of sesame oil and the comb growth measured in the same fashion as when the injection method is employed. The growth response curve can be found in the literature[5]. The lower portion of the curve is almost linear, showing the relationship $x = 0.5\ y$ where y is the growth of the comb in millimeters and x the daily dose per bird of androsterone expressed as micrograms. The limits for normal individuals have not as yet been established but it seems probable that, expressed as androsterone, the level of blood androgens is similar to that of urinary androgens.

Determination of Estrogens in Urine

A 24 hour specimen of urine is acidified, using 5 per cent by volume of concentrated sulfuric acid. It is then hydrolyzed by boiling for 2 hours. The estrogens are extracted and concentrated by the technic described for the extraction of androgens. The extract is finally taken up in 30 cc. of sesame oil. This oil is then assayed by a modification of the method of Gustavson and D'Amour[9]. Spayed mature rats which have been observed for several weeks and are known not to have gone into estrus are used for the assay. One rat unit is that amount of hormone which will bring 50 per cent of the rats into estrus 72 hours following injection. The rat is considered to be in estrus when the predominating cell obtained in a vaginal smear is a non-nucleated cornified epithelial cell.

For most clinical purposes it is not necessary to know exactly how much estrogenic material is being excreted. It is therefore our custom to make a preliminary assay using 2 rats at each of three levels. One pair of rats receives 0.75 cc. of oil each, another pair 1.5 cc., and the third 3.0 cc. From the results obtained the approximate level of estrogenic excretion can be determined. If none or only one of the rats reacts with a positive vaginal smear, it is probable that the patient being studied has ovarian deficiency.

If more accurate results are required, sufficient material is still available to make possible an assay using 10 rats at a level indicated by the preliminary assay. Each of the 10 rats receives the same dose. The following table is taken from the data of Gustavson and

D'Amour and indicates the probable number of rat units which each rat receives as interpreted from the number of rats which came into estrus. If one rat comes into estrus the dose was 0.5 rat unit. If all 10 rats come into estrus the dose was at least 3 units. The corresponding values dependent upon the number of rats coming into estrus are shown in the following table:

Number of Rats Coming Into Estrus	*Number of Rat Units Each Rat Receives*
2	0.73
3	0.83
4	0.92
5	1.00
6	1.1
7	1.2
8	1.4
9	1.8

Obviously, then, the following formula can be used to calculate the amount of hormone an individual is excreting:

$$\frac{\text{No. of units per rat} \times 30}{\text{Dose per rat}} = \text{rat units per 24 hours.}$$

Normal women excrete from 20 to more than 40 rat units in 24 hours.

Chemical methods for the determination of estrogens have been available for some time. Most of these, however, have not been sufficiently sensitive to be satisfactory for the study of normal women or those with hypogonadism. A recent method published by Kober[10] has much merit and may obviate the necessity of the cumbersome and expensive bio-assay procedure.

The Friedman Test

The technic and interpretation of the Friedman[11] modification of the Aschheim-Zondek[12] test as employed in this institution was described in this journal by Mr. W. K. Cuyler[13]. As a test for pregnancy 12 cc. of the urine to be tested is injected into the marginal ear vein of a mature female rabbit which has been isolated for three weeks. Parous rabbits rather than virgins are preferred. Twenty-four hours later the ovaries are examined. The gonadotropic hormone which is found in the urine of pregnant women will bring about the formation of mature follicles, ruptured follicles, hemorrhagic follicles, and fresh corpora lutea. In a high percentage of cases the presence of ruptured or hemorrhagic follicles indicates pregnancy. Several mature follicles are usually seen in the normal ovary of a rabbit.

An excessive amount of gonadotropic hormone may occur in conditions other than pregnancy, i.e., pituitary or chorionic tumors, teratomata of the testes, and hypogonadal states such as occur at the female climacteric or in the male in testicular deficiency. In some instances of this sort there is insufficient hormone to cause a frankly positive Friedman test when the technic outlined previously is employed. If larger quantities of urine are used and the injections continued over a longer period, these slight excesses can be demonstrated in the rabbit. For example, if 4 cc. of urine are injected three times daily on two consecutive days and the rabbit is examined on the third day, positive reactions will be obtained from urines which do not give positive reactions when the simpler technic is employed. Occasionally one encounters urines which are so toxic that the rabbits do not survive the injection. Such urines should be chilled, filtered, and carefully neutralized before injection. The difficulty can sometimes be overcome by administering the urine in numerous small doses and if necessary by precipitating the hormone with alcohol as described in the method for the quantitative assay of prolans. In detecting small quantities of gonadotropic hormone by this method the experienced observer will notice congestion and swelling of the uterine horns which is indicative of ovarian stimulation. When the test is used as a test for pregnancy one should not expect a positive reaction less than three weeks after conception. The output of gonadotropic hormone in the urine of pregnant women increases rapidly subsequent to that time and is invariably quite high in the sixth week. A negative Friedman test is a very reliable indication that an individual is not pregnant. A positive Friedman test indicates an excessive excretion of gonadotropic hormone and must be interpreted in the light of the numerous possible causes.

Quantitative Determinations of Gonadotropic Hormone

In assaying urines for the determination of pituitary or pituitary-like hormones, the method employed depends somewhat on the concentration of the hormone in the urine. When the concentration is very high the urine can be assayed directly. If, however, the content is low, as for example in the normal individual, methods of concentration must be employed. Several such methods have been published[14,15,16,17]. At present we are employing ethyl alcohol as a precipitant. Four volumes of 95 per cent alcohol are added to one volume of urine. This mixture is placed in the refrigerator overnight and the supernatant liquid removed by means of a syphon. The residue is centrifugalized, desiccated, and extracted with water, and the assay is carried out on the aqueous extract. The method of Heller, Lauson and Sevringhaus[18] is a satisfactory method in that the animal supply houses are able to furnish imma-

ture rats on demand and it is therefore unnecessary to maintain an animal colony. This method involves the use of 21 day old female rats. Each rat is injected once on the first day, twice on each of four subsequent days, and is autopsied on the 26th day of life. The uterus and ovaries are removed and weighed after expelling all fluid from the uterus. The extent of increase in weight over the controls is a measure of the amount of gonadotropic hormone present. A 24 hour specimen of urine from a normal young man will usually yield sufficient hormone to cause a marked stimulation in one rat. Men over sixty who are apparently normal have been observed to excrete larger amounts of gonadotropic hormone.

Semen Examinations

Some endocrinological disorders as well as other causes will result in partial or complete aspermia. Moench[19] and Hotchkiss[20] have discussed these problems in considerable detail. The methods employed in this laboratory in the examination of semen are as follows: The patient is requested to collect all the semen produced on the first ejaculation following at least three days of continence. The semen should be collected in a glass container because the chemical substances contained in rubber are injurious to the spermatozoa. The semen should be brought to the laboratory as quickly as possible after collection and should be kept as close to body temperature as possible until examination. The specimen is first measured for volume and for pH. It is then examined grossly for activity, the approximate percentage of spermatozoa immotile, slightly motile, and actively motile being estimated. The time of receiving the specimen is noted and the specimen is stored at room temperature. A microscopic examination is made at once and repeated subsequent observations are then made to ascertain the viability. Live sperms will be found in the semen of normal individuals several hours after collection; viability is frequently maintained for more than 18 hours.

The technic employed in determining the number of sperms is similar to that used in counting blood cells. About 500,000,000 sperms are found in the ejaculate of a normal individual. If the number of sperms in the specimen seems high a red count pipette is employed for dilution and the areas designed for counting white cells are used. One may multiply by 500 to get the number of sperms per cubic millimeter and then by 1000 to get the number per cubic centimeter. If the count is low a white count pipette should be used and the areas designed for white cell counts utilized. One should multiply by 50 to get the number of spermatozoa per cubic millimeter and then by 1000 to get the number per

cubic centimeter. The diluting fluid employed is 1 per cent formaldehyde and 5 per cent sodium bicarbonate.

In studying the morphology of the sperms, a smear is stained by the technic followed by Moench[21]. Slides are air-dried, fixed by heat, and then treated with a 10 per cent solution of chlorazene for ½ to 2 minutes. They are then washed with water and 95 per cent alcohol and stained for 1½ to 5 minutes with a modified Williams stain which is made in the following manner:

Ziehl-Neehaon's carbolfuchsin — 50 parts
Saturated alcoholic sol. bluish eosin — 25 parts
95% alcohol
These materials are mixed and filtered.

After staining, the slide is washed with distilled water and counter stained for 1 to 5 seconds with methylene blue (saturated alcoholic solution of methylene blue diluted to one third of strength with distilled water). It is finally washed with distilled water.

Examination of Vaginal Smears

The epithelium of the vagina gives an indication of the activity of the ovaries. This has been studied by Papanicolaou[22] and Papanicolaou and Shorr[23]. The smear is made from fluid removed from the vagina with a glass pipette, using a heavy rubber bulb to furnish the suction. The tip of the pipette should be placed 5 to 6 cm. within the vaginal orifice. The fluid is spread as a heavy film on the slide and is immediately fixed in equal parts of 95 per cent alcohol and ether. After fixation for at least one half hour it is passed successively through 80 per cent alcohol, 70 per cent alcohol, 50 per cent alcohol, and distilled water. It is then stained for five minutes with Ehrlich's hematoxylin, washed in water for 15 minutes, and stained for 4 minutes with 0.5 per cent eosin. It is washed with water, stained with 0.5 per cent water blue for 5 minutes and again rinsed. The slide is then carried through alcohol water solutions until it is finally placed in absolute alcohol and xylol and mounted in balsam or gum damar.

In most instances in order to determine the exact type of smear in a given individual, repeated examinations must be made. During the cycle the smear changes in a fashion similar to that in lower mammals. In the normal individual during the so-called copulatory period which probably corresponds to the time of ovulation, the predominant cell is a cornified epithelial cell. The test is a valuable aid in determining whether or not a dose of estrogen is adequate for the treatment of a patient whose symptoms are atypical and a poor guide.

Determination of Iodine

The iodine to be measured is converted to iodide by digestion in an alkaline solution and separated from interfering substances by distillation from acid solution. It is then oxidized to iodate, which in turn is used to liberate iodine from an excess of added iodide in acid solution. The iodine is titrated with sodium thiosulfate. In the analysis of tissues or materials containing only a small proportion of organic matter, the alcoholic extraction may be omitted. In foods where it may be necessary to use large samples to obtain the 2 or 3 micrograms necessary for accurate estimation, the fusion may be conducted in several crucibles and the alcoholic extracts combined.

Fusion: 10 cc. of blood (or an amount of material containing about 2 to 3 micrograms of iodine) are boiled with 12 cc. of saturated potassium hydroxide solution in a 300 cc. nickel crucible until foaming ceases. The Bunsen flame must be carefully manipulated at the beginning to control excessive foaming; goggles should be worn as a protection against possible spatter due to careless manipulation. Organic material may be washed down the sides of the crucibles with a little water. The crucible is placed in the muffle furnace at 250° for 30 minutes (or less) to drive off gases. The temperature is then raised to 360° over a period of 30 minutes, and allowed to remain at this temperature another 10 minutes, after which the crucible is removed.

Extraction: Sufficient water is added to the fused mass to form a fluid paste on cooling. This is extracted by thorough stirring with 25 cc. of 95 per cent ethyl alcohol, which is decanted from the sludge into another 300 cc. nickel crucible. The extraction is then repeated four more times with 10 cc. portions of alcohol. To the combined extracts 0.5 cc. of saturated potassium hydroxide is added. The alcohol is evaporated on a steam bath and the crucible placed in the muffle furnace at 385° for 15 minutes.

Distillation: The ash is dissolved in water and transferred quantitatively to a modified 50 cc. Claissen flask which has the auxiliary tubulation sealed, thus eliminating the use of a rubber stopper and reducing the condensing surface. The end of the tube leading from the condenser goes to the bottom of a 50 cc. extraction flask which contains water just sufficient to cover the end of the condenser tube, 0.2 cc. of a 3 per cent solution of sulfuric acid, and 0.2 cc. of a 10 per cent solution of sodium bisulfite. To the contents of the Claissen flask are added quickly 2 cc. of 50 per cent solution of sulfuric acid, 1 drop of a 10 per cent solution of ferric sulfate, and 2 cc. of a 3 per cent solution of hydrogen peroxide (superoxol diluted to make a 3 per cent solution). More acid is added if necessary to make the solution definitely acid, as

indicated by the presence or absence of ferric hydroxide. A glass bead is added to prevent bumping. The flask is immediately closed with the stopper and dropping funnel, the outlet of which has been drawn to a point. The contents of the flask are then boiled vigorously over a microburner, care being taken, however, to avoid flooding of the side arm of the Claissen flask. One or two additional 2 cc. portions of 3 per cent hydrogen peroxide are added through the dropping funnel during the distillation. Heating is discontinued during these additions to avoid carrying hydrogen peroxide over with the distillate. The distillation is discontinued when the volume in the Claissen flask is reduced to about 5 cc. or when sulfates begin to crystallize on the side of the flask.

The extraction flask is placed on a wire gauze with asbestos center and the contents are boiled gently for 2 minutes to expel carbon dioxide and sulfur dioxide, a glass bead being used to prevent bumping. The solution is immediately made alkaline to litmus paper with 10 per cent potassium hydroxide; this should not require more than 3 drops. The solution is then carefully boiled down to a volume of 5 or 6 cc.; 1 drop of methyl orange is added, and the solution is neutralized by the addition of 3 per cent sulfuric acid. Two drops of acid in excess are then added along with 5 drops of bromine water which should cause the solution upon shaking to turn yellow immediately. It is then boiled down very cautiously to about 2 cc. and cooled on ice. This should require from 3 to 5 minutes in order completely to remove excess bromine with a minimum loss of iodine.

Titration: One drop of a 1 per cent solution of starch and 2 drops of a 1 per cent solution of potassium iodide are added and titration is carried out with a 0.001 normal solution of sodium thiosulfate which is delivered from a microburette or a 0.2 cc. pipette graduated to 0.001 cc. A blank (usually 0 and never more than 0.02 cc.) should be run on all reagents.

Calculation: One cc. of 0.001 normal sodium bisulfite is equivalent to 21.2 (micrograms) of iodine. When 10 cc. of blood are used as described:

(Titration - Blank) x 212 = micrograms iodine p\ 100 cc. blood.

Interpretation: Normal blood contains usually fro.i 7 to 14 micrograms of iodine per 100 cc., of which one half or less is alcohol insoluble. This fraction is increased in hyperthyroidism and may represent active thyroid substance. Eighteen per cent or less of the total iodine in normal blood is probably in an inorganic form. This is increased by the administration of iodine. In cretinism the total amount of iodine decreases. In hyperthyroidism it is usually increased.

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SODIUM AND CHLORIDE RETENTION IN ADDISON'S DISEASE TREATED WITH DESOXYCORTICOSTERONE ACETATE

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The new synthetic adrenal cortical hormone, desoxycorticosterone acetate, promises to be of great assistance in the clinical management of Addison's disease. It was produced by Reichstein[1] and is made from stigmasterol. Its clinical value has not yet been established although the investigation of it is progressing in various parts of this country and abroad. Levy Simpson[2] reported its use over a short period in two cases of Addison's disease with encouraging although not conclusive results.

At present, we do not feel justified in attempting to draw conclusions regarding its value in the cases of Addison's disease we have treated. Some observations presented here indicate that the material causes a rather marked diminution in excretion of sodium and chloride. In this respect, it duplicates the metabolic effect which has been proved for adrenal cortical extract[3].

It should be noted that other steroids are known to produce a similar result. For example, Kenyon[4] has shown that urinary sodium and chlorides are retained in the body in cases of testicular deficiency treated with testosterone propionate and our own observations in one case confirm this. The fact that corticosterone causes sodium and chloride retention is therefore not to be considered as[3] evidence that it will duplicate other effects of cortical extracts.

The material has been tested in the following manner on two patients who had clinical Addison's disease. Both were subjected to the salt deprivation test described by Cutler, Power, and Wilder[5]. This test may be briefly described as follows: A diet is supplied which is calculated to yield a daily intake of 0.95 gm. of chlorides, 0.59 gm. of sodium, and 4.1 gm. of potassium. On the evening of the first and the morning of the second day, additional potassium citrate is given in the amount of 0.92 gm. per kilogram of body weight. Free drinking of water is encouraged on the first day. On the second day 40 cc. per kilogram are given and on the third, 20 cc. per kilogram are given before 11 a. m.

The urine is collected in three specimens, two during 12 hour periods and one in a 4 hour period. The first specimen is from 8 a. m. to 8 p. m. of the second day, the second from 8 p. m. the second day to 8 a. m. of the third day, and the last specimen is from 8 a. m. to 12 noon of the third day. Blood sodium and potassium levels are estimated, fasting the second day of the test and at 10 a. m. on the morning of the third day.

It is unnecessary to describe the results of the test in detail here. It is sufficient to say that the most striking changes are observed in the sodium and chloride excretion on the morning of the third day in cases of adrenal deficiency. The results are shown to greatest advantage as milligrams per 100 cc. of urine, and the chloride excretion shows a wider deviation from normal than the sodium. The potassium excretion is not changed in any way to make it of clinical value.

In seven cases of Addison's disease in Cutler's report, the sodium excretion on the third day of the test varied from 165 to 282 mg. per 100 cc. while in 28 control cases the excretion was between 6 and 85 mg. per 100 cc. at the same period. The chloride excretion during this period in the cases of Addison's disease was 229 to 356 mg. per 100 cc. while in those not having Addison's disease, it varied between 17 and 141 mg. per 100 cc.

The first of our two cases is that of a woman, 35 years of age, who had symptoms typical of Addison's disease. She had no abnormal pigmentation but she did have calcification of the right adrenal. Previously she had shown a typical clinical response to eschatin* and sodium chloride therapy.

TABLE 1

	Blood (*mg. per 100 cc.*)			*Urine* (*mg. per 100 cc.*)			
Date	*Sod.*	*Pot.*	*Chlor.*	*Sod.*	*Pot.*	*Chlor.*	*Remarks*
Nov. 29	371″	19″		114	137	220	Test 12 hrs.
30	371′	17′	544′	22	86	180	Test 4 hrs.
Dec. 12							C.S. 10 mg.
13	352″	17″					C.S. 10 mg.
14				24	105	20	Test 12 hrs. C.S. 15 mg.
15	362′	17′		14	85	17	Test 4 hrs. C.S. 5 mg.

″—fasting
′—mid a.m.

Table 1 shows the results of a test similar in all respects to the one described above except that only the second twelve hour specimen of

* Eschatin is adrenal cortical extract, Parke, Davis & Co.

urine was examined in each test. She had had no eschatin or extra sodium chloride for more than one month.

It will be seen that the chloride excretion levels are within the range described above for Addison's disease but the urinary sodium is not.

Between the time of the first and the second test, the diet was calculated to contain between 0.8 and 1.9 grams of potassium daily and from 0.7 to 1.5 grams of sodium. No sodium chloride or adrenal extract was used in treatment during this period but a potassium tolerance test, using 3.9 grams of potassium citrate on December 5 and 5.4 grams on December 6, was used. She was also given 8 grams of potassium citrate daily on December 9, 10, and 11, which precipitated marked evidence of Addison's disease.

Desoxycorticosterone marked C.S. in the table was given as shown. The striking fall in sodium and chloride excretion is evident during the second test period.

The second case is that of a man, 38 years of age, who had typical Addison's disease of moderate severity with weakness, gastro-intestinal symptoms, arterial hypotension, and mucosal hyperpigmentation.

TABLE 2

	Blood (*mg. per 100 cc.*)			*Urine* (*mg. per 100 cc.*)			
Date	*Sod.*	*Pot.*	*Chlor.*	*Sod.*	*Pot.*	*Chlor.*	*Remarks*
Jan. 4	356″	18.9″		178	293	465	12 hr. test
4				113	372	400	12 hr. test
5	347′	16.7′	495′	55	272	425	4 hr. test
5	Injections begun at 1 p. m.						C.S. 10 mg.
6							C.S. 20 mg.
7	357″	22.9″	511″	34	259	120	C.S. 15 mg. 12 hr. test
7				23	228	75	12 hr. test
8	344′	19.1′		17	86	50	4 hr. test

″—fasting
′—mid a.m.

Table 2 indicates the results of the salt restriction test before and after the administration of desoxycorticosterone acetate.

Summary

In two cases of Addison's disease, administration of desoxycorticosterone acetate caused a striking fall in sodium and chloride excretion similar to that known to result from adrenal cortical extracts.

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IRRADIATION IN THE TREATMENT OF CANCER OF THE BREAST

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There are a few ancient writings which discuss medical subjects including cancer of the breast, the earliest dating back to about 2000 years before Christ. After printing processes were developed, considerably more was written about methods of treatment and it is apparent that cancer of the breast has been treated by caustics, cautery, and excision through many centuries. When Halsted wrote his classical report and described his radical operation he reviewed the literature prior to 1897 and came to the conclusion that up to that time no woman with cancer of the breast had been cured. Following his report and that of Willy Meyer, all other methods of treatment were discarded and radical operations were generally employed.

These radical operations have become quite standardized by skilled and experienced surgeons. In them, the mammary gland, fascia, muscles, and axillary contents are removed "en masse." These are the anatomical limits of the most radical operative procedure recognized as justifiable, but cancer of the breast unfortunately is not always confined within these limitations. It extends beyond the anatomical boundaries of the most radical surgical procedure in a majority of cases as is evidenced by the fact that the general average of surgical curability of cancer of the breast, on the basis of the five year survival rate, is approximately thirty per cent. This average was compiled from reports which eminent surgeons have published since 1900. This means that in seventy per cent of the cases the disease had extended beyond the possibility of removal by the time operations were performed. It may also be concluded that with the modern radical technic, surgeons have reached the limit of the possibility of curing a higher proportion of cases on the basis of the extent of operation alone. This is indicated by their reports in the literature which show that the average five year survival rate has been the same during the past twenty years as it was during the twenty years preceding and immediately following the advent of the radical technic.

It is also interesting to note from reports in the literature that the five year survival rate has varied from fifteen to fifty per cent. These reports were made by skilled and experienced surgeons who operated under the best of conditions and employed a technic which is now quite standardized. If this assumption is justifiable, then a logical explanation of the wide variation in results is due to differences in the types of cases selected for operation, some surgeons operating upon more advanced cases and therefore obtaining a lower percentage of survivals

than those who do not operate upon women in advanced stages of disease.

If a thirty per cent five year survival rate has been the average result obtained by the standardized radical operative technic by the most skilled surgeons operating under the most favorable conditions, then the medical profession should endeavor to find other methods of treatment to supplement operation. The only modern method known to be effective in the treatment of cancer is irradiation by radium and roentgen rays.

If the literature is studied to determine what may be the efficacy of irradiation in the treatment of cancer of the breast, it will be found that there are differences of opinion among surgeons. Of course, radiologists are almost unanimously convinced of the usefulness of their methods of treatment. But in almost every instance when surgeons have reported that irradiation has been of no benefit and have based their conclusions upon comparisons of series of cases in which irradiation was given before or following operations with series in which there was no irradiation at all, it is obvious that the irradiated series contained a considerably greater proportion of cases in which the disease was advanced. Many surgeons have included in the irradiated series cases in which treatment was given any time subsequent to operation, primarily because of recurrences or metastases and not solely to prevent extension of the disease. This is unjust because the treatment of recurrences or metastases presents a different problem and the prognosis is entirely unlike that for primary or early, localized malignant tumors.

Deductions based upon disproportions between early and advanced cases are not justifiable. The only way that logical conclusions can be reached about the benefits of one method of treatment over another is to compare series containing equal proportions of cases in the same stages of disease.

A number of suggestions have been made for classifying cases of cancer of the breast both from the clinical and histological aspects. The latter method has been found to be uncertain because cancers of the breast are not often histologically homogeneous but most are heterogeneous. Indeed, several types of morphology may be found in almost every tumor. Another objection to classifying tumors on the histological basis is that, although this may indicate what the rate of growth or dissemination may be, it tells nothing about the actual extent of the disease which is the most important consideration from the standpoint of prognosis.

Therefore, it would seem that the best method of classifying cases of cancer of the breast for statistical comparisons would be to take into consideration both the clinical and the pathological evidences of the

extent of the disease. A method of classification or grouping of cases on this basis which we have found to be of value not only for statistical purposes but also to indicate what therapeutic procedures are preferable may be stated as follows:

Group I: Cases in which freely movable tumors are definitely localized in the breast, the skin is not involved, and no metastases are present in the axillary lymph glands.

Group II: Cases in which freely movable tumors are definitely localized in the breast, the skin is not involved, but there are metastases in only a few axillary lymph glands.

Group III: Cases in which there is diffuse involvement of the breast, the skin is involved, edematous or ulcerated or with multiple nodules, and metastases are present in numerous axillary lymph glands or other tissues.

In order to illustrate how this method of grouping may be applied, I selected a series of 405 cases of cancer of the breast operated upon by Dr. George Crile. Of these, there was sufficient information about 373 to classify them according to the plan suggested. It was found that about 30 per cent fell into Group I, 25 per cent into Group II, and 45 per cent into Group III. No doubt the same relative proportions would be found in each group in any large series of cases. It should be noted that in 70 per cent of cases axillary metastases were present (Groups II and III).

When an analysis was made to determine the surgical curability based upon the five year survival rates, it was found that in a series of 170 cases in which operation was the only treatment, none of the patients having had irradiation at any time, almost 100 per cent of patients in Group I lived for five years. This might be expected because in this group the cancers were well localized, not having extended even to the axillary lymph glands and therefore all the neoplastic tissue was excisable.

Of the Group II cases in which operation alone was performed, about 50 per cent of the patients survived five years. This indicates that, in an equal proportion of cases, the entire neoplastic process could not be removed and therefore the patients succumbed. Of the Group III cases no patient survived five years without evidence of cancer. Certain conclusions may be drawn from Group II and Group III cases. First, if only a few lymph glands are involved from a cancer of the breast, the neoplastic disease is removable by operation alone in about one-half of the cases because approximately one-half of the patients in this category survived five years. This may mean either that cancer tissue was left locally or in the axilla or that distant metastases had developed prior to operation. Secondly, it has been stated that almost one-half of

all patients are in advanced stages of disease at the time of operation (Group III) and none are cured. This indicates that radical operations upon patients in this category should not be performed but other methods of treatment should be employed instead.

Some surgeons have been skeptical about the advantages of irradiation given immediately after operation because, in certain instances, those unfamiliar with radiological procedures have drawn erroneous conclusions as a result of incorrect analyses of statistics. A few have stated that irradiation not only was of no benefit but that the proportion of patients who died following such treatment was higher than those who did not receive irradiation. Of course, such conclusions must be based upon disproportions between the advanced and early cases in the series used for comparison. It is obvious that irradiation cannot spontaneously inject neoplastic cells before or after operations for cancer of the breast and that if recurrences or metastases do develop the disease must have been present at the time of treatment which may have been as ineffectual as the operation.

Many radiologists have published statistics about their results but, unfortunately, these usually appear in publications that seldom are read by surgeons. It will be found by studying many of these reports that the average five year survival rate for patients treated immediately after operations for cancer of the breast has been 40 per cent by methods employed some years ago. With new developments in technic, this percentage has increased. This shows a distinct benefit as compared with the average of 30 per cent by operation alone.

However, all these statistics were based upon unclassified cases and the wisdom of grouping cases for comparisons has been discussed. A study of our series of 235 cases in which postoperative roentgenotherapy was given immediately following operation for cancer of the breast shows that 230 could be grouped on the basis of the criteria previously mentioned. Of these, 25.2 per cent fell into Group I, 30.4 per cent in Group II, and 44.4 per cent into Group III. It was found that irradiation in Group I cases was of no benefit. This could be expected because almost 100 per cent of these patients are curable by operation alone. Approximately 70 per cent of the patients whose carcinomas were classified as Group II and who were given roentgenotherapy survived five years which was a distinct improvement over the number of patients in the same group but who had operation alone; only 50 per cent of these patients lived five years. Of the patients in Group III, 10 per cent of those who received irradiation survived five years but none was without evidence of cancer. However, in this group the proportion of patients who survived each yearly period up to five was higher than those having operation alone.

It may justifiably be concluded from a comparison of these two series of cases that there was benefit from roentgenotherapy given postoperatively, not necessarily because a greater proportion of patients were cured of cancer of the breast but because some lived longer due to delay in extension of the disease in some cases. Of course, such a statistical analysis does not take into account the benefits of irradiation for the relief of distress from metastases. There is no mathematical basis by which to estimate palliation.

The results of treatment of the patients in the two series grouped according to the extent of the disease indicate what procedures should be employed in the treatment of cancer of the breast.

A woman with a small localized tumor in the breast should be operated upon immediately. It may be difficult in many cases to distinguish between benign or malignant tumors on the basis of clinical findings alone. The tumor should be excised completely and examined microscopically at once. If the tumor is benign, no further operative procedure is necessary. If the tumor proves to be malignant, a more extensive operation should be performed. A simple mastectomy may suffice occasionally if the tumor is very definitely and conclusively found to be well localized. However, in a majority of cases it will be necessary to perform a radical operation and to explore the axilla by complete dissection in order to disclose the extent of the disease.

After removal, the breast and each axillary node should be examined carefully by a pathologist. If no axillary metastases are found the patient will be in Group I or Stage I, and the prognosis will be good because experience proves that almost 100 per cent of the patients in this category are cured by operation alone. Roentgenotherapy given postoperatively is not indicated because all the malignant tissue has been removed. But when metastases are found in even a few axillary lymph nodes, the chances of the patient surviving for five years will be 50 per cent by operation alone. These are Group II cases. Naturally, the number of axillary nodes involved does make a difference in the prognosis. But patients with axillary metastases should receive roentgenotherapy immediately postoperatively in the hope of destroying or delaying the progress of the disease because some neoplastic tissue will remain in one-half of such cases and there is no conclusive way of determining in any case whether or not cancer remains.

The advanced Group III cases offer quite a different problem. A large proportion of these patients will present clinical evidences that the disease is extensive and incurable by the most radical surgical procedures. It should be noted that there is a difference between "operability" and "curability." Technically, it may not be difficult to perform a radical mastectomy but the question of whether the operation will

benefit or cure the patient should be paramount. It has been shown that no patient with manifestations of incurability has survived free from cancer for five years; indeed, there is good evidence which indicates that the lives of patients with advanced cancer of the breast actually are shortened by radical operations. Since patients with clinical evidences of incurability cannot be cured by the most radical surgical procedures, there is no justifiable reason for operating upon them except in very rare instances where a minor operation is performed for purely esthetic reasons. These patients should be given the benefit of irradiation by roentgen rays or combined with radium according to the individual indications. At least this treatment will not shorten life; on the contrary, in many instances it will cause tumors and axillary or supraclavicular metastases to disappear completely, thus definitely prolonging the lives of many patients although a cure may not be effected. It should be recalled that 45 per cent of all patients on whom operation was performed in our series were in Group III and had extensive disease and were therefore incurable. But this proportion of cases does not include some who were considered to be in too far advanced stages of the disease to justify operations. In all probability more than half of the patients who have come to surgeons in the past were incurable by operation.

Sometimes it will be impossible to determine on the basis of clinical examinations alone which patients are incurable by operation. Some patients may have rather small tumors, the skin may not be involved, there may be no evidence of axillary metastases but after operation numerous lymph nodes may be found with metastases or other evidences of incurability. These patients should receive roentgenotherapy immediately postoperatively. On the other hand there are clinical manifestations which should be sought and patients with any of them should not be operated upon but instead irradiation should be given. These evidences of incurability may be tabulated in the following manner:

The skin: Edema
Browny red, indurative and inflammatory
Multiple nodules
Ulcerative

The breast: Edema
Diffuse infiltration
Multiple tumors
Fixation of breast or tumor to chest wall

Metastases: Axillary nodes, numerous, extremely involved, unfixed
Supraclavicular nodes or edema of arm
Distant metastases (lungs alone or other organs).

Conclusions

1. Series of cases of cancer of the breast to be analyzed for statistical purposes should be grouped according to a suggested plan which is based upon the extent of the disease found to be present in each case.

2. Patients with tumors of the breast but with no clinical evidences of incurable cancer should be operated upon immediately.

3. If cancer of the breast is found on immediate microscopic examination, radical mastectomy should be performed in the majority of cases.

4. If no metastases are found to be present on microscopic examination of all axillary lymph nodes removed, no other treatment is necessary and almost 100 per cent of the patients will survive five years (Group I).

5. If axillary metastases are found in only a few axillary lymph glands, about 50 per cent of the patients will survive five years if operation is the only treatment. Immediate postoperative roentgenotherapy should be given to such patients, in which case about 70 per cent will survive five years (Group II).

6. If numerous axillary lymph nodes show metastases, no patient will survive five years free from cancer if operation is the only treatment. Roentgenotherapy should be given immediately to delay extension of the disease and prolong life.

7. Patients with the clinical evidences of incurability which are enumerated should not be operated upon but treated by irradiation alone.

8. Improved technics offer even better results from irradiation than were possible five or more years ago.

RECENT ADVANCES IN THE TREATMENT OF OBSTRUCTIVE JAUNDICE

GEORGE CRILE, JR., M. D.

In addition to the hazards incident to all surgery of the upper abdomen, operations on the biliary tract, performed in the presence of obstructive jaundice, are associated with special risks arising as the result of the biliary obstruction. The danger of secondary hemorrhage, of liver failure, and of the development of cholangeitis is always present in these operations. In the past year, however, certain advances in the prophylaxis and treatment of these complications have been made and we have good reason to believe that a striking reduction in the postoperative mortality rate of jaundiced patients will soon be observed.

The liver is invariably damaged by long-standing obstruction of the biliary tract. A marked hemorrhagic tendency is often present in patients with this condition and they are in poor condition to withstand a major surgical procedure. It is therefore not surprising to find the surgical mortality higher in patients with obstructive jaundice than in unjaundiced patients subjected to similar surgical procedures.

Hemorrhage is the greatest single cause of death, one-third of all postoperative deaths being attributable to this cause. Other causes of death in the order of their frequency are pneumonia, liver failure, cardiac failure, and a varied assortment of incidental complications (Table 1).

TABLE 1

ANALYSIS OF CAUSES OF DEATH

Cause of Death	*Per Cent*
Hemorrhage	34
Pneumonia	20
Liver failure	14
Heart failure	8
Extensive metastases	6
Peritonitis	3
Duodenal fistula	3
Pyloric obstruction	3
Stricture of common duct	3
Uremia	3
Unknown cause	3
	100

Secondary hemorrhage has been the most common complication following operations on patients with obstructive jaundice. In our experience hemorrhage has occurred most frequently on the first day, nine of the patients in this series of 100 cases having bled in the first 24 hours after operation. Three patients bled on the third day, and one each on the fourth, fifth, sixth, eighth, tenth, eleventh, twelfth, and nineteenth days.

Another troublesome complication following operations for obstructive jaundice has been the development of cholangeitis. This occurred to some extent in 29 per cent of the operations in which anastomoses between the biliary and gastro-intestinal tracts were performed. There were, however, no postoperative hospital deaths attributable to cholangeitis.

Liver failure has been a rare but more serious complication following operations on the biliary tract in jaundiced patients. This complication occurred in 6 per cent of all the cases. Liver failure was observed most frequently following operations for carcinoma of the pancreas and when it occurred it usually was fatal.

The Bleeding Tendency in Jaundice

Until recently, the fear of postoperative hemorrhage has handicapped the surgeon in his attempts to relieve patients with obstructive jaundice. However, recent developments in the diagnosis and treatment of this hemorrhagic tendency will unquestionably result in a marked diminution in hemorrhage as a postoperative complication and will open the field for a more radical surgical attack not only on stones in the common bile duct but also on neoplasms of the bile ducts, the ampulla of Vater, and the head of the pancreas.

A review of the physiology of the clotting of blood shows that prothrombin, thromboplastin, and calcium unite to form thrombin. This in turn unites with fibrinogen so that fibrin is formed.

$$\left.\begin{array}{l}\text{Prothrombin}\\ \text{Thromboplastin}\\ \text{Calcium}\end{array}\right\rangle \text{Thrombin} + \text{Fibrinogen} = \text{Fibrin}$$

It has been well established that the cause of the hemorrhagic tendency in jaundice is a deficiency in prothrombin. A prothrombin deficiency likewise occurs in animals having complete external biliary fistulae. Thus the tendency to bleed is the result of a failure of the gastro-intesinal tract, in the absence of bile, to absorb certain extraneous substances[1]. The older belief that the bleeding was the result of excessive amounts of bile in the blood stream must therefore be discarded.

Hitherto, this bleeding tendency has been difficult to determine before operation. Ordinary tests of the bleeding and clotting time have been unsatisfactory. The bleeding time by the Lee-White method often indicates that a hemorrhagic tendency will occur but this test has not been very satisfactory. By the Lee-White method, venous blood is used, the blood is placed in tubes, and the time of clotting is recorded. Any time over eight minutes is considered to be abnormal. The Lee-White coagulation time is prolonged in only about one-third of the cases in which a hemorrhagic tendency exists.

Ivy[2] has recently reported a technic for bleeding time which is alleged to be of value in the study of the hemorrhagic tendency in jaundice. By this method a tourniquet is applied to the arm in order to overcome capillary resistance. The bleeding time is then measured in the usual way. It is quite true that the bleeding time by this method is almost always prolonged in deep jaundice but the bleeding time tends to be prolonged in proportion to the severity of the jaundice rather than in relation to the tendency of the patient to bleed. This test, therefore, gives very little more information than does the icteric index.

Quick's[3] method for the determination of the prothrombin clotting time has been proved to be a valuable aid in the diagnosis of a hemorrhagic tendency. In this test all the factors which are necessary for the coagulation of the blood are added in excess and a specimen of blood plasma is then added and the time for clotting is recorded. Specifically, the blood is oxalated and the plasma obtained. The plasma is then mixed with an emulsion of dried rabbit brain to supply an excess of thromboplastin. Calcium chloride is added to this mixture. The number of seconds that it takes at a temperature of 37.5° C. for a clot to form is recorded as the prothrombin time. Normal values are about 20 seconds and bleeding tendencies in the presence of jaundice are not apparent when the prothrombin clotting time is less than 40 seconds. More accurate information as to the presence of a latent hemorrhagic tendency in patients who have a prothrombin clotting time of less than 40 seconds can be obtained by diluting the serum by half and then determining if there will be a further prolongation of the prothrombin clotting time.

A bleeding tendency does not occur until the prothrombin level reaches approximately 20 per cent of normal. It is thus apparent why a jaundiced patient who has an apparently normal prothrombin clotting time will suddenly begin to bleed after an operation. If the amount of prothrombin in the blood was above the critical level before operation, dilution of the prothrombin as a result of blood loss at the time of operation may result in a diminution of the prothrombin below the critical level and in the appearance of a hemorrhagic tendency.

Naffziger and Carr[1] have conducted some interesting investigations on the influence of high protein diets in jaundice. They find that in the presence of jaundice a high protein diet results in an elevation of the sulfur content of the blood to nearly double its normal level. They have also noticed that when jaundiced dogs are fed on a meat diet, hemorrhage and death occurs promptly, but if a similar group of dogs is fed on a high carbohydrate diet, life is prolonged approximately three times.

Walters[5] and others have suggested that bleeding tendencies can be diminished by the administration of calcium chloride or calcium gluconate intravenously. Although calcium in vitro seems to diminish the clotting time of the blood in jaundiced patients, clinically the administration of calcium has not proved to be of much value except to alleviate the troublesome pruritus.

The most promising treatment of the hemorrhagic tendency in jaundice is that recently reported by Butt, Snell, and Osterberg[6] of the Mayo Clinic. This group became interested in the reports of Dam and his coworkers[7] on the hemorrhagic tendency which developed in chicks fed on a diet deficient in certain fat soluble compounds but adequate in respect to vitamins A, B_1, B_2, C, and D and in total fat and cholesterol. Dam was able to demonstrate that the hemorrhagic tendency was promptly corrected by the administration of a substance found in the unsaponifiable non-sterol fraction of hogs' liver fat and in alfalfa. This substance he designated as vitamin K.

Heymann and his coworkers[8] have shown that fats and sterols are not absorbed from the intestines of a dog in the presence of an external biliary fistula and Heymann was able to show that viosterol was not absorbed after experimental ligation of the common duct. It is probable, therefore, that the hemorrhagic tendency in obstructive jaundice is due to a failure to absorb the anti-coagulation vitamin designated as K.

A third interesting piece of experimental work has been done by Roderick[9] who has shown that animals fed on spoiled sweet clover hay developed a hemorrhagic tendency. As yet the exact cause of this tendency has not been determined, although it is known that it is the result of a prothrombin deficiency. Whether the spoiled hay interferes with the absorption of vitamin K, or whether the formation of vitamin K is interfered with by damage to the liver from some agent present in the spoiled hay, is not known.

Snell[10] states that we are justified in concluding, "(1) that the hemorrhagic state in jaundice is attributable to a deficiency of prothrombin which in turn is due to failure of absorption or utilization of some substance normally present in the diet which requires bile for its absorption; (2) that this substance may be the hypothetical coagulation vitamin

(vitamin K), and (3) that additional toxic factors may deplete the supply of prothrombin, as in sweet clover disease and necrosis of the liver caused by chloroform." Theoretically, 20 mg. of vitamin K should be an adequate daily dose for man, but ten times this dose, approximately 200 mg. daily, is the dose that Butt and Snell have been using.

Greaves and Schmidt[11] demonstrated that bile salts serve as a carrier for fat-soluble vitamins and therefore in cases in which bile is not entering the intestinal tract it is essential to administer them along with the vitamin K in order to insure its absorption.

Through the courtesy of Dr. Butt of the Mayo Clinic, we were able to obtain a supply of vitamin K and have confirmed his observations on its efficacy in the control of hemorrhage in jaundiced patients. In one case, a deeply jaundiced patient on Dr. T. E. Jones' Service, there had been profuse bleeding from the uterus, the mucous membranes, and the incision. The prothrombin clotting time was 60 seconds and the patient's condition was critical. Within 12 hours after the administration of 200 mg. of vitamin K by mouth along with 6 "Kapseals of S-Bile"

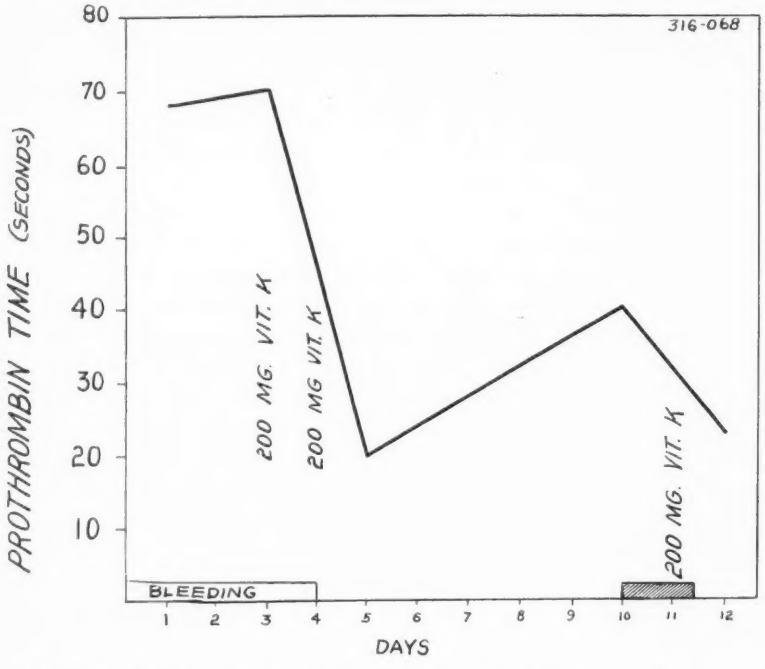

CHART 1: Chart showing the reduction in prothrombin clotting time and cessation of bleeding following the administration of vitamin K.

(Parke, Davis & Co.) all bleeding had stopped. On the following day 200 mg. of vitamin K was again given and the prothrombin clotting time was found to have fallen to normal (Chart 1).

An essential point is that vitamin K will not reduce the prothrombin clotting time unless bile is in the intestinal tract or unless it is given along with bile salts. One of Butt and Snell's charts demonstrates this very clearly, vitamin K having been given alone for one week with no change in the clotting time and then, when bile salts were added to the vitamin K, the prothrombin time promptly fell from 110 to 30.[6]

Blood transfusion has also been a valuable agent in the control of the hemorrhagic tendency in jaundice. Normal blood contains a great excess of prothrombin (approximately 5 times the amount necessary for coagulation) and consequently the administration of one or more blood transfusions may raise the prothrombin level to a point where bleeding will be avoided or stopped. The bleeding is generally not from large vessels and in our experience has occurred most commonly into the incision or into the gastro-intestinal tract. Not infrequently the bleeding may occur from all the mucous membranes. If sufficient blood to make up the prothrombin deficiency can be given, the bleeding should always stop. Inasmuch as the majority of hemorrhages have occurred within the first 24 hours after operation, it is well to give a blood transfusion before and another immediately after the operation. But an equal number of hemorrhages have occurred later in convalescence and therefore a third transfusion should be given about the third or fourth day after the effects of the initial transfusions have worn off. Since the discovery of vitamin K, however, there is less indication for blood transfusion.

Liver Failure

Although liver failure has been directly responsible for a relatively small proportion of the deaths following operations on jaundiced patients, it is not unlikely that many terminal pneumonias and some of the postoperative hemorrhages have been the indirect result of damage to the liver. It is therefore essential that deeply jaundiced patients have a low protein and high carbohydrate diet for some days prior to operation. In cases with marked liver damage glucose should be administered intravenously by the continuous drip method for 24 hours prior to operation and for the first two or three days afterwards or until the patient is again able to assimilate a high carbohydrate diet.

We have demonstrated clearly in hyperthyroidism that glucose given intravenously by the continuous drip method is much more effective in controlling the postoperative thyroid reaction than is the intermittent administration of large quantities of glucose solution. When the glucose is given intermittently it is usually given too rapidly and a great deal of it is eliminated by the kidneys. The same applies in obstructive jaundice and if the maximum assimilation of the glucose is to be obtained and the liver is to be given maximum protection the glucose should be given continuously. In a recent case of obstructive jaundice the patient began to hiccough on the second postoperative day and on the third postoperative day he became confused and delirious. His condition appeared desperate; blood transfusion was given in order to prevent any tendency to bleed, but it was not until a continuous drip of glucose was given intravenously that the delirium cleared, the hiccoughs finally ceased, the liver again began to function and the bile which had been pale and had been excreted through the T-tube in very small amounts rapidly returned to normal quality and quantity. This patient was practically afebrile during the period of his delirium and there was no evidence of pulmonary or intraperitoneal complication. The toxic reaction was certainly the result of liver failure and the dramatic recovery was in all probability directly attributable to the administration of large quantities of glucose intravenously and continuously.

Cholangeitis

A second complication of surgery in the biliary tract is the development of cholangeitis, a complication which has occurred following 29 per cent of the operations in which anastomoses were made between the biliary tract and the gastro-intestinal tract. Hitherto, we have had no logical means by which to combat this type of infection.

It has recently been demonstrated in the experimental laboratory that sulfanilamide is excreted in the bile. External biliary fistulae were made in dogs, large doses of sulfanilamide were given to these animals, and we were able to recover sulfanilamide in the bile in amounts equivalent to that present in the blood. Clinically, we have tried sulfanilamide in several cases of cholangeitis with promising results. In one case an anastomosis between the gallbladder and the jejunum had been performed, a cholecystoduodenostomy or cholecystogastrostomy being rendered impossible by an extensive carcinoma of the stomach which had invaded the common duct and resulted in jaundice. After operation, as is often the case when the lower portion of the intestinal tract is anastomosed to the biliary system, severe cholangeitis with chills, fever, and jaundice developed. The patient was treated with sulfanilamide

and within 48 hours the chills and fever had subsided and the temperature returned to normal. We have since observed similar responses to sulfanilamide in other patients with cholangeitis. It therefore appears that sulfanilamide may be as valuable an antiseptic in the biliary tract as it has proved to be in certain stubborn B. coli infections of the urinary tract.

The Surgical Treatment of Carcinoma of the Pancreas and Bile Ducts

In our experience, the surgical mortality following cholecystogastrostomy or cholecystenterostomy performed to relieve obstruction of the bile ducts by carcinoma of the pancreas has been slightly lower than that of exploratory operations or cholecystostomies performed for the same condition. The incidence of fatal hemorrhage after operation was four times as high in those patients having merely drainage of the gallbladder or exploratory operations and the deaths from liver failure were twice as frequent. In other words, we have evidence to indicate that the more extensive surgical procedures involving anastomosis between the biliary tract and the gastro-intestinal tract carry with them a lower mortality rate than do the palliative operations in which the abdomen is only explored or the gallbladder is drained.

The lower mortality rate associated with the more extensive operations can best be explained by the fact that in an anastomosis operation obstruction of the liver is always removed and with the bile returning to the gastro-intestinal tract the patient's ability to assimilate food is increased and his convalescence is therefore more rapid and complete. To be sure, one must remember that when only exploratory operations were performed they were often on the patients who were in the poorest condition to withstand major surgery. But it is nevertheless clear, in view of the results that have been obtained, that the anastomosis operations are well justified. The pruritus is relieved and in many instances the patients have lived in comfort for from one to two years after operation.

Until Whipple[12] described a radical two-stage operation for carcinoma of the ampulla of Vater and for carcinoma of the pancreas and proved that the external secretion of the pancreas was not necessary for the maintenance of life and health, obstructive jaundice due to malignancy of the head of the pancreas was considered to be hopeless. The main problem had always been the successful reimplantation of the pancreatic ducts into the gastro-intestinal tract. Attempts to anastomose the pancreatic duct to the intestinal tract too often resulted in a pancreatic and intestinal fistula with digestion of the surrounding tissues and event-

ual death of the patient. Successful radical resection of the head of the pancreas was not therefore performed until recent times.

Carcinoma of the pancreas does not necessarily metastasize early. In 60 per cent of the cases in this series there were no demonstrable metastases at the time of operation. Likewise, in 60 per cent of the cases of carcinoma of the bile ducts and in the one case of carcinoma of the ampulla of Vater no demonstrable metastases were present. In many of these cases the carcinoma was apparently limited to the field that could be excised by a radical operation. In other words, a large number of these patients had a possibility of being cured by radical surgery.

Although most autopsy statistics show that only about 10 per cent of all carcinomas of the pancreas fail to show metastasis[13] at the time of the patient's death, a much higher percentage of carcinomas of the ampulla of Vater and of the bile ducts have failed to metastasize by the time the patient died. Moreover, many of these patients died without surgical intervention and should therefore be considered to be later cases than the surgical cases generally seen.

In view of these figures and the success which radical operations on carcinoma of the head of the pancreas are obtaining, I believe we should be less pessimistic in regard to the prognosis in this disease. The least that we can do is to perform an anastomosis between the biliary tract and the intestinal tract so that the patients will obtain relief of their symptoms and so that, in the rare case where the lesion is a pancreatitis rather than a carcinoma, the patients will obtain a permanent cure. One patient in our series lived two years following an anastomosis between the intestinal tract and the biliary tract, ultimately dying of carcinoma of the pancreas but being perfectly well for a year after operation, then having a gastro-enterostomy because of obstruction of the duodenum, and again being well for nearly a year before finally succumbing to carcinoma.

Twelve cases of radical resection of the head of the pancreas have already been reported, six patients have survived operation, and one of these (reported by Whipple) is still alive and well nearly three years after the original operation.

I have recently performed a radical two-stage resection of the head of the pancreas on a patient with a well-differentiated duct type of carcinoma which was apparently limited to the head of the pancreas[14]. The excision of the tumor appeared to be complete. It is now eight months since operation, the patient is back at work, is gaining weight, feels well, and in this case I believe that the prognosis is at least hopeful.

With the recent development of vitamin K to correct the hemorrhagic tendency in jaundiced patients, by means of continuous drip of in-

travenous glucose used to combat liver failure, and with the advent of sulfanilamide in the treatment of cholangeitis, radical surgery of the pancreas and biliary tract will unquestionably receive a new impetus.

Summary

1. Postoperative hemorrhage has been the most common and most serious complication following operations on patients with obstructive jaundice.

2. The hemorrhagic tendency in jaundice is the result of a diminution of the prothrombin content of the blood.

3. The prothrombin clotting time is the most reliable method of determining the presence of a hemorrhagic tendency.

4. The administration of vitamin K and bile salts restores the prothrombin clotting time to normal and corrects the hemorrhagic tendency of jaundiced patients.

5. The most effective protection against liver failure is the *continuous* intravenous administration of large quantities of a 10 per cent solution of glucose both before and after operation.

6. Sulfanilamide has been effective in the control of cholangeitis.

7. It is probable that the indications for radical surgery of the biliary tract and carcinoma of the head of the pancreas will be extended as a result of the recent technical and physiological developments in the field of obstructive jaundice.

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DIFFERENTIAL DIAGNOSIS OF COMMON PERIPHERAL VASCULAR DISEASES

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Due to advances in medical therapeutics there has been a definite increase in the life span of man, and thereby an increase in the incidence of degenerative diseases is seen.

The most common changes are those seen in general arteriosclerosis which may or may not be associated with diabetes mellitus. Arteriosclerotic changes may occur in any part of the vascular tree and quite frequently affect the smaller peripheral vessels. As the circulation is decreased, symptoms occur that frequently bring the patient to the physician.

Thrombo-angiitis obliterans, which is also known as Buerger's disease, is an inflammatory reaction that occurs in the arteries and veins of the extremities resulting in formation of thrombi and occlusion of these vessels.

Another disease in this group is clinically known as Raynaud's disease or symmetrical gangrene. In this entity intermittent spasm takes place in the digital arteries. This is associated with typical changes in color and in some instances the condition progresses to necrosis and local gangrene.

Arteriosclerosis, with or without diabetes mellitus, thrombo-angiitis obliterans, and Raynaud's disease constitute the greatest percentage of peripheral vascular disturbances seen by the physician.

ETIOLOGY

Even after extensive research and clinical investigation no definite causative agent can be named for arteriosclerosis. Prolonged and intensive activity may play a part, infectious diseases such as typhoid fever, and syphilis, diabetes, and prostatitis may be contributing factors.

The relationship between arteriosclerosis and diabetes is well recognized. A child with diabetes may show signs of arteriosclerosis. Essential hypertension also has a definite association with this process.

The etiology of thrombo-angiitis obliterans is still unknown. The frequent occurrence of migratory phlebitis makes it seem that it may be of an infectious nature. Tobacco has been looked upon as an etiologic agent and in many instances these patients use a great deal of tobacco; on the other hand, it also occurs in those who do not use tobacco. It has been thought that this disease has occurred mostly in Polish and Russian Jews, but today it is known that it may occur in any race.

In Raynaud's disease the etiology is also unknown, although it is now recognized that the occurrence of peripheral vasoconstriction which

may lead to gangrene and death of the extremity is a distinctly sympathetic affection or vasomotor imbalance.

Pathology

Arteriosclerosis is a general disease involving the large and small arteries in proliferative and degenerative processes. The pathology is much the same regardless of its appearance in the large or small vessels although in the smaller arteries it is apt to cause more diffuse proliferation in the intima. As the disease progresses, deposits of fat appear in the cells of the intima, new connective tissue cells form, and also new elastic tissue. While this process is going on there may be deposits of fat in the muscle cells of the media. As the process advances, the intima thickens and the fatty areas may break down and become necrotic. Thrombi may form over the necrotic areas of the intima and thus cause obstruction.

The end result of these changes is that the arteries lose their elasticity and become hard, rigid, and tortuous. With proliferation of the intima in the smaller vessels, narrowing of the lumen occurs and thus the circulation through the vessel is diminished or obliterated. After narrowing of the vessel, the final occlusion by secondary thrombosis gives rise to the senile and diabetic forms of gangrene.

It is recognized that a relationship exists between arteriosclerosis and diabetes mellitus. In spite of the marked advance in therapy of diabetes mellitus, the pathologic process in the vessels has not been arrested. McKittrick and Root[1] found that the chief difference between these two conditions lies in the relative amounts of intimal and medial change. In the diabetic limb with obliterative vascular disease, there exists an extensive amount of endothelial proliferation and fatty deposition in the intima, the lumen of the vessel being filled with lipoid packed cells, new connective tissue, and leukocytes. While a moderate degree of medial sclerosis with calcium deposition is a common finding, the striking feature is the change in the intima.

Buerger[2] described chronologically the pathological picture of thrombo-angiitis as follows: "An acute inflammatory lesion with occlusive thrombosis, the formation of miliary giant cell foci, the stage of organization or healing, with disappearance of miliary giant cell foci, the organization and canalization of the clot, the disappearance of inflammatory products, and the development of fibrotic tissue in the adventitia that binds together the artery, vein, and nerves."

Allen[3] believes that "the process is one of inflammation, producing early thrombosis which is localized and which often becomes canalized. The process becomes chronic and has tendencies to heal as it spreads to

other portions of the vessels or may become quiescent later to flare up again or even apparently remain healed in certain instances."

With vasoconstriction of the peripheral vessels in Raynaud's disease, asphyxia to tissues occurs. This may be of a temporary nature with slight pathological change. However, if sufficiently intense, changes occur in the arterioles, terminating in superficial gangrene or ulceration of the tips of the fingers or toes.

Diagnosis

In many instances these peripheral vascular diseases can be diagnosed without any great difficulty. This is especially true when all the classical symptoms appear; however, some will not be so simple and every diagnostic measure must be utilized.

A general and routine medical history and physical examination are essential when examining these patients. In the general history, special note is made of the findings of the cardiac system. In addition, we use a special form on which we record information and findings relative to the peripheral vascular disease. On the special form the following information is recorded: age, sex, occupation, birth place, and nationality.

When eliciting the present complaints, pain will be a prominent symptom. During the early stages pain may be entirely in the feet, and treatment may be concentrated there for fallen arches or some other foot difficulty. It may appear while the patient is walking or exercising only to disappear entirely after a period of rest. This type of pain is well known as intermittent claudication.

The patient may be unable to sleep or rest due to pain which is known as rest pain. The distress may be of a burning or aching nature in the digits, being produced by exposure to cold or some emotional upset. If this appears, vasospasm should be considered.

Inquiry should be made whether it is difficult to keep the extremities warm. The patient usually comments that the hands or feet are cold. Notation should be made of the presence of calluses, ulcerations, eczema, and the condition of the toenails. A brief summary of the onset and course should be obtained.

A family history of arteriosclerosis, diabetes mellitus, syphilis, nervous disorders, hypersensitiveness, or angina pectoris may be of importance. A personal history of injury, frost bite, chilblains, phlebitis, foci of infection, or use of ergot should be noted. The amount and form of tobacco used, such as cigarettes, pipe, and cigars, should be listed in detail. Changes in the color of the skin of the feet or hands may be noted by the patient.

The diagnosis of Raynaud's disease is practically made when, after exposure to cold or an emotional upset, the skin becomes dead white and then changes to a blue or purplish or bluish black. This reaction can be reproduced by immersing the hand in cold water.

Changes in color should be noted in the extremities because frequently early changes in the vessels can be diagnosed. Ischemia of the extremities is perhaps the most important diagnostic sign in the circulatory disturbances of the extremities. Plantar ischemia can be demonstrated by using Samuels[4] test. The patient lies on his back with the lower extremities elevated to an angle of 45 degrees or more. The patient then rapidly flexes and extends the feet, using the ankle joints as pivots. If the arterial circulation is intact, there will be no deviation from the normal pink tinge of the plantar surfaces even after prolonged ankle motion. In the presence of arterial occlusion, however, even of minimal extent, a decided pallor soon develops.

Rubor can best be demonstrated when the extremity is pendant. In advanced peripheral vascular changes the rubor appears following a few seconds of pendancy. If mild changes have occurred, only the fore part of the foot may be involved and in the more advanced cases it may involve the foot entirely and sometimes extend up the leg.

Cyanosis in an extremity is usually a sign of grave danger of gangrene, especially if it does not disappear on finger pressure.

Much information can be obtained by examining the peripheral pulses. In the upper extremity, the axillary brachial and radial pulses can be readily palpated and in the lower extremity the femoral, popliteal, posterior tibial, and dorsalis pedis arteries are easily palpated. In a small percentage of patients, the dorsalis pedis and posterior tibial may be absent. This, however, is not definite evidence of obstructive peripheral vascular disease unless other pathology can be demonstrated.

The blood pressure and blood counts should also be noted. The histamine test is of value in determining the superficial cutaneous circulation and is especially helpful when amputation of an extremity is being considered. This test may be done by one of two methods: (1) Place a drop of histamine acid phosphate on the cleansed area of the skin and then scratch with the point of a hypodermic needle as is done in a vaccination or, (2) inject the drop intradermally. The test can be made above the ankle, below the knee, above the knee, or on the upper part of the thigh.

If there is no involvement in the circulation, the reaction obtained will be a red spot succeeded by a wheal and this in turn will be surrounded by a flare. Such a reaction will develop within five minutes. If the

circulation is below normal the appearance of the wheal and flare will be much slower or may not appear at all.

Various tests have been utilized to determine the presence of vasospasm. In each test the principle is the same, that is, release of the constricting influence of the sympathetic nerves to the peripheral vessels will produce a dilatation of these vessels if they are capable of dilating. If the vessels dilate, an increased blood supply will result and thus elevate the temperature of the skin. To make such determinations, a skin thermometer is necessary. To make an accurate test for vasospasm, the patient is placed in a room with the temperature between 70° and 74° F. The extremities are exposed to the room temperature for one hour before the first readings are taken. One of the methods for removing the constricting influence is then used. The simplest of these was described by Landis and Gibbon[5]. After readings are made on the feet, the hands and forearms are immersed in a water bath with a temperature of approximately 110° F. for 35 minutes and readings are again taken. In normal reactions the temperature of the toes will be elevated to 90° or 92° F.

With the blanket test described by Coller and Maddock[6], the patient is exposed for one hour in a room at 70° F. and readings are made. The patient is then wrapped in three heavy blankets for one hour and readings are again taken.

Injection of the peripheral nerve or the use of spinal anesthesia are also used to study the skin temperature to rule out vasospasm. Novocain is injected into the posterior tibial nerve and plantar anesthesia of the foot results. The skin temperature of the ball of the great toe is taken before and after the injection. The difference in temperature will indicate the amount of peripheral dilatation obtained. Spinal anesthesia also removes the constricting influence in the extremities but this procedure carries with it some risk and requires hospitalization.

The oscillometer is an instrument used to determine the elasticity of the arteries of the extremities and takes the place of the palpating finger in the examination of the peripheral arterial pulsations. A needle swings along a graduated scale which gives quantitative information concerning the amplitude of the peripheral pulses. With this instrument, pulses that were not palpable to the examining finger can be demonstrated.

Roentgen studies of the extremities may be of value to demonstrate the presence of calcium deposits in the arteries. These pictures do not, however, give information as to the amount of obstruction in the vessels. They may be of value to help confirm the diagnosis of a marked arteriosclerosis.

Differential Diagnosis

The differentiation of thrombo-angiitis obliterans and arteriosclerosis will at times present a difficult problem. In both instances the symptoms are produced by the occluding process in the vessels. Intermittent claudication, pain, ischemia, rubor, decreased or absent arterial pulsations, and gangrene are common in both diseases.

Thrombo-angiitis obliterans usually occurs in males between the ages of 20 and 45 years. A history of excessive smoking of cigarettes is generally obtained. In about 40 per cent of the patients, the presence of or a history of a migrating phlebitis is noted. Migrating phlebitis may particularly involve the external and internal saphenous veins and may be preceded by the appearance of subcuticular red spots or nodules on the leg which are tender and hard upon palpation. Although any race may be affected, it is predominant in the Russian and Polish Jews.

Arteriosclerosis generally occurs in patients in the older age group, the changes usually not being apparent until the age of 50 is reached. If diabetes is present, the symptoms appear at an earlier age and calcification of the peripheral arteries is much more intense than in the uncomplicated arteriosclerosis.

Silbert[7] suggests the following outline for differentiation of the two diseases:

Thrombo-angiitis obliterans	Arteriosclerosis
Appears younger than his age	Appears older than his age
Hair normally pigmented	Hair usually gray
No arcus senilis	Arcus senilis frequently present
Retinal arteries normal	Retinal arteries usually sclerotic
Blood pressure usually low	Blood pressure often high
Radial and temporal vessels soft	Radial and temporal vessels thickened and hard
Upper extremities frequently involved	Upper extremities seldom involved
Femoral arteries frequently closed	Femoral arteries seldom closed
No calcification of vessels on X-ray	Calcification of vessels on X-ray frequently seen
Blood volume usually diminished	Blood volume usually normal
Symptoms of coronary artery sclerosis rare	Symptoms of coronary artery sclerosis frequent
Aorta appears normal on X-ray	Aorta sometimes appears elongated on X-ray
Albuminuria rare	Albuminuria not uncommon
History of migrating phlebitis frequent	History of migrating phlebitis rare

Raynaud's disease belongs in the vasospastic group. It is characterized usually by a symmetrical vasospastic disturbance of all extremities and sometimes the tips of the nose and ears. The disease shows a pre-

dilection for women between 18 and 40 years of age. It predominates in young, thin women who are unusually sensitive to cold. The onset is usually sudden with blanching, commonly of one or more fingers or toes. Due to the local syncope there is severe pain or paresthesia and the member will have a "dead" feeling. The appearance is that of marble-like pallor and coldness. It may last from a few minutes to hours and disappear. The color may change to a blue or purplish or bluish-black (cyanosis). Following this reaction blebs may develop which may last for months. If the bleb proceeds to gangrene it breaks down, leaving an ulcerated area which finally cicatrizes, or a dark scab may develop and become detached. After a series of attacks, the fingers are seen to be very thin, hard and tapering, and the nails present trophic disturbance.

Gangrene of the fingers and toes is frequently seen in polycythemia vera. A local thrombosis occurs in the arteries due to the high viscosity of the blood.

The appearance of the patient is usually quite striking. The face and ears exhibit a peculiar dusky redness seen in no other disease. When the patient is exposed to cold temperatures cyanosis is very marked in the hands and face. The excessive blood volume may cause dyspnea, palpitation or a sense of cardiac oppression. Weakness or easy fatigability may be present. Examination of the eye grounds reveals engorged and tortuous arteries. The red blood cells and blood volume is greatly increased.

Usually marked pallor can be demonstrated on elevation of an affected extremity and when pendant, marked engorgement occurs. If gangrene is produced it is usually in the toes and fingers and is definitely demarcated.

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SOME OBSERVATIONS IN THE TREATMENT OF ACUTE ENCEPHALITIS BY ROENTGEN THERAPY AND TYPHOID SHOCK REACTIONS

JOHN TUCKER, M. D.

Since the great pandemic of influenza from 1916 to 1920, renewed interest has been shown in the diagnosis and treatment of acute and chronic encephalitis. As experience has increased in the management of this condition we have found that a great many cases do not conform to the classical symptomatology that was first described by von Economo in 1917[1]. While the severe, acute manifestations may consist of "somnolence, ophthalmoplegia and profound asthenia," the onset in most of our cases has not been so typical.

For the sake of accuracy the lethargic type of encephalitis must be differentiated particularly from such conditions as benign lymphocytic choriomeningitis, disseminated encephalomyelitis, and acute multiple sclerosis. Of even greater importance is the necessity for the careful differential diagnosis of spontaneous subarachnoid or intracranial hemorrhage, subdural hematoma, brain tumor, brain abscess, atypical types of meningitis, or hysterical cataleptic states. Likewise, the cerebral manifestations of general disease may simulate acute encephalitis such as diabetic coma, uremia, metastatic brain lesions, or syphilis of the central nervous system. If a careful clinical and laboratory study is made in all cases, the lesion can usually be placed in its proper category.

At the Clinic, among the early acute cases of encephalitis, we have found that the most common symptoms are headache, somnolence, coma, oculomotor disturbances, nausea or vomiting, and fatigue. In certain cases we often find severe vertigo, disturbances of speech, convulsions, monoplegia or hemiplegia. Not infrequently our study of these patients must include not only the usual clinical or neurological examination with various blood chemical and serological studies and the determination of spinal fluid pressures, but in more difficult cases an encephalogram becomes necessary. The subarachnoid fluid is studied for total protein, globulin, differential cell count, colloidal gold, and Wassermann reaction. With the aid of such data, we are able to determine, as a rule, whether the case requires medical or surgical treatment and whether the disease is of virus or bacterial etiology.

When we consider the nature of the neurotrophic virus, we can understand, to some extent, why treatment has been so ineffectual. This pathogenic substance, whether bacterial or chemical, is an obligate parasite which appears to live and reproduce within the grey matter of the central nervous system. Likewise, the cellular protoplasm of the

host acts as a barrier to viricidal substances such as antibodies and chemicals. It is known that the disease may progress in spite of a high titer of specific antibody in the blood. These observations enable us to understand to some extent why the usual remedies are not specific.

In the second report of the Matheson Commission[2], we find a discussion of more than fifty different drugs that have been employed in the treatment of acute encephalitis and encephalomyelitis. These include such preparations as salicylates, iodides, arsenicals, silver, antimony, mercury, quinine, methylene blue, strychnine, sulphur, ephedrine, benzedrine sulphate, atropine, scopolamine, pilocarpine, vaccines, convalescent sera, and many other miscellaneous preparations. This large array of medicinal substances bears mute testimony to the fact that, as yet, no specific method of attack has been developed. We have been shooting at a hidden target in the hope that, by controlling symptoms to some extent, we may be able to stay the relentless progress of this disease. While many of the patients with the milder types of encephalitis may recover spontaneously, in many instances the disease progresses to death or to hopeless invalidism.

In the Clinic we have been impressed by the fact that there are two therapeutic procedures which hold considerable promise of success. The first is nonspecific protein shock with intravenous injections of typhoid vaccine which may serve to "shake up" the cells of the body and thus to attentuate or destroy the neurotrophic virus. The second method, deep roentgen therapy, may act in a similar manner. Dr. Portmann believes that it serves to dispose lymphocytic infiltration with the liberation of antibodies as it apparently does in other inflammatory conditions. Both these methods have been used individually or together in a group of selected cases. While our experience in either instance has not been sufficient in number or time to justify a statistical report, the results, in general, have been most gratifying. Further study of these cases is necessary to determine whether the benefit is permanent or whether relapses or postencephalitis complications will appear. We must also take into consideration the knowledge that complete recovery may occur spontaneously in about 25 per cent of the cases, while the death rate is slightly in excess of 38 per cent. In the remaining 37 per cent the complications may be mild or severe[3].

Typhoid Shock Therapy

At present it seems apparent to us that the improvement which may come from typhoid shock reactions will be more striking and more lasting if the patient is seen and treated early, probably within the first week of the disease. On the other hand, we have failed to produce permanent improvement not only in late cases of encephalitis when

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host acts as a barrier to viricidal substances such as antibodies and chemicals. It is known that the disease may progress in spite of a high titer of specific antibody in the blood. These observations enable us to understand to some extent why the usual remedies are not specific.

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sequelae have appeared but also in most cases of encephalomyelitis or cases that were regarded first as encephalomyelitis and later proved to be acute multiple sclerosis. In general, typhoid shock appears to be most effective when used in conjunction with deep roentgen therapy of the central nervous system.

We employ a modification of the method first employed by Howard[4]. Twenty-five million typhoid organisms from any standard vaccine are diluted with about 10 cc. of fresh sterile normal saline solution and given intravenously. As soon as the temperature is normal for 24 hours, a second dose, double in amount of vaccine, is again given. The third dose is double the second and so on until six reactions of chills and fever have been given. We always wait for normal temperature before administering the next dose. The maximum temperature rise is usually between 101° and 104° F.

Roentgen Therapy

The use of deep roentgen therapy in the treatment of acute encephalitis is not a new procedure. A few reports have appeared in foreign and American literature, some with favorable and other with adverse comments. Under the supervision of Dr. U. V. Portmann this therapy has proved to be a simple and harmless method of treatment. Amelioration of the patient's symptoms has occurred, often before the full course of radiation has been completed. In some instances two or even three series of treatments have been employed. The number of exposures as well as the dose used is varied somewhat with the type of case and the patient's response to the first few treatments. As will be evident in the case reports, the combination of roentgen irradiation and typhoid shock has been satisfactory. We have no satisfactory explanation for this observation. It may be that the fever and roentgen therapy build up the cellular resistance to the parasite or serve to make antibodies more effective within cells. We have observed no harmful effects from treatment with either x-ray or typhoid shock. The former usually causes depilation of the scalp which is only temporary. The hair returns, usually curly, within a few weeks.

The following case histories, given in tabloid form, will serve to illustrate some of our experiences with these two forms of therapy.

Postinfluenzal Encephalitis. Typhoid Shock Therapy. Recovery

Case 1: Woman, 29 years of age, admitted February 2, 1937.

Complaints: Sleepiness, headache, staggering.

History: "Influenza" in August, 1936, with acute vertex and occipital headache.

Two months later, blurring of vision and slight drooping of eyelids, ataxia, mental depression, sleepiness, and irritability when awake.

Significant Findings: Nystagmus upward and laterally, normal optic discs, slight drooping of eyelids, sluggish mentality, absent abdominal reflexes, ataxic gait.

Sinuses and teeth normal.

Simple hypochromic anemia.

Wassermann reaction and undulant fever agglutination negative.

Spinal fluid pressure normal.

Laboratory tests normal.

No fever.

Treatment: Typhoid shock reactions. Good febrile response.

Results: Immediate improvement at the termination of the reactions.

Four months: Normal physical findings.

Two years: No recurrence.

Comment: It would appear that this patient has responded very well to typhoid vaccine given intravenously. The absence of a recurrence or any sequelae over a two year period is encouraging.

Acute Encephalitis. Roentgen Therapy. Recovery

Case 2: Man, 45 years of age. Admitted August 6, 1938.

Complaints: Headache, attacks of vomiting, jumbled speech—one month.

History: No acute respiratory infection. Gradual onset of increasingly severe headaches, lethargy, vomiting, incoherent speech, and incontinence of urine without fever.

Significant Findings: Optic discs normal, lethargy, sluggish deep reflexes, positive abdominal reflexes.

Roentgen Examination of Skull: Pineal calcification in midline.

Spinal Puncture: Pressure 220 mm., clear fluid, 3 cells, negative for globulin, 120 mg. protein, negative Wasserman reaction and colloidal gold.

Encephalogram: No air in either ventricle; cortical fluid pathways normal.

Roentgen Examination of Chest: Normal, no metastases seen.

Laboratory Tests: Wassermann and undulant fever agglutination negative. Urine normal.

No fever.

Treatment: Deep roentgen therapy. Nine exposures to right and left sides of skull alternately during a period of 10 days.

Results: Six weeks after treatment, normal physical findings.

Patient felt well except slight mental sluggishness.

Ten weeks: Normal except slight urinary urgency.

Five months: Normal.

Comment: The acute symptoms in this case were of short duration. The response to roentgen therapy was very striking and satisfactory.

Acute Encephalitis. Typhoid Vaccine and Roentgen Therapy. Recovery

Case 3: Woman, 28 years of age. Admitted April 15, 1938.

Complaints: Blurred vision, sleepiness, headache.

History: "Grippe," fever, and chills, November, 1937.

Significant Findings: Normal fundi and visual fields.
Internal squint left eye (paresis sixth cranial nerve, left).
Spinal fluid normal—three separate punctures.
Roentgen examination: Paranasal sinuses normal.
Laboratory tests of blood and urine normal.
No fever.

Treatment: Typhoid shock. Six satisfactory reactions, April, 1938.
Typhoid shock, second series, August, 1938.
Roentgen therapy to skull, 4 exposures, December, 1938.
Roentgen therapy, second course, January, 1939.

Results: Apparently complete recovery two months after the last treatment.

Comment: This patient had had severe symptoms for three and one-half months before therapy was begun. She failed to experience satisfactory relief of her headache and squint until she was given a second course of roentgen therapy. After the first course of typhoid there was a partial remission which lasted for four months. She derived no benefit from the second series of typhoid injections. At the present time she is gaining weight, looks entirely well, and has no complaints.

Acute Encephalitis Following Chicken-Pox and Measles. Roentgen and Typhoid Therapy. Recovery

Case 4: Child, 8 years of age. Admitted March 29, 1938.

Complaint: Coma.

History: Five weeks previously, rhinitis, cough and chicken-pox. No fever.
Three weeks previously, measles, slight fever.
Ten days previously, sudden onset of fever to 104° F. with vomiting.
Eight days previously, convulsions, delirium, screaming followed by listlessness, and finally semi-coma.

Significant Findings: Dilated, sluggish pupils; fundi normal.
Apathy with no response to mild painful stimuli.
Chewed and swallowed only on command.
Reflexes: Absent patellar and Achilles. Left lower abdominal reflexes positive. Bilateral Babinski.
Paralysis of right eighth and left sixth cranial nerves following spinal puncture.
Urine: Trace of albumin, blood normal.

Spinal fluid: Pressure, 140 mm. water, clear, 2 cells, 25 mg. protein. Negative for globulin, colloidal gold, and Wassermann.

Treatment: Roentgen therapy: Five exposures in 5 days, March 30, 1938. Typhoid shock therapy. Five injections with good response, April 14, 1938.

Results: Complete recovery with no residuals. Five months.

Comment: Symptoms of acute encephalitis rather than of encephalomyelitis developed shortly after the attacks of chicken-pox and measles. Immediately after the x-ray therapy was completed the patient became fully conscious but curious motor manifestations developed which always followed a definite pattern and were repeated over and over throughout the day. Suddenly she would sit up, flop herself down on her right side, then turn over to the left side, and promptly sit up again. The cycle was completed in about one-half minute and was immediately begun again. During meals she could be diverted from these movements and during sleep under sedatives she was quiet. After several days of these distressing symptoms a course of typhoid shock therapy was started. Following the third injection, her motor restlessness disappeared and she made a rapid recovery to normal health. While it is probable that this apparent irritation of the globus pallidus of the mid brain would have responded to a second course of roentgen therapy, she recovered so well after three typhoid chills that this proved to be adequate treatment. This remarkable patient has remained entirely well for five months.

Conclusions

The use of deep roentgen and typhoid shock therapy appears to be distinctly helpful and possibly curative in the treatment of acute encephalitis in its early stages. Both Dr. W. James Gardner of the Neurosurgical Division and Dr. U. V. Portmann of the Department of Roentgen Therapy have felt very much encouraged with the results in their cases. Of the two methods, the best results follow radiation. However, observations on a large number of patients over a long period of time is necessary before any positive statements can be made. We do believe that no other form of therapy has been so satisfactory in the treatment of acute encephalitis.

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BRONCHOSCOPY IN THE DIAGNOSIS AND TREATMENT OF BRONCHIECTASIS

PAUL M. MOORE, JR., M. D.

Bronchiectasis is a chronic, debilitating disease characterized by dilatation of the smaller bronchi and copious, foul, purulent sputum. It robs the patient of his appetite, strength, and social contacts. In its advanced stage it is incurable. When less advanced it is curable only by lobectomy. If recognized sufficiently early it may be cured or at least its progress may be arrested by less radical means.

Certain definite factors have been quite well established in the etiology of bronchiectasis:

(1). Bronchopneumonia, sometimes unrecognized in infancy, may result in contracting scar tissue which produces dilatation of the bronchi[1,2].

(2). Localized atelectasis due to a mucous plug or aspirated foreign body in a bronchus may produce a dilatation of the bronchi in the affected area[3,4,5,6,7,8]. If the obstruction is removed early and the atelectatic areas become aerated, the dilatations of the bronchi may disappear[9,10]. If the atelectasis is overlooked and the obstruction is not removed the dilatations will remain[11].

(3). Watson and Kibler[12] have recently stated that the most common cause is allergy, the sequence of events being basal allergic bronchitis followed by atelectasis which in turn is followed by dilatation of the bronchi.

(4). There is also a congenital form which may go unrecognized until it becomes infected.

Attempts have been made to establish a single infecting organism as the principal cause of the disease. Those most frequently accused are the Bacillus influenzae, the fusospirillum, and Treponema microdentium and Treponema macrodentium[13]. That these organisms play an important part in some cases is without question but they have not been found in a sufficient percentage of the reported cases to assign an all-important rôle to them. A rather large unreported series of cases which I observed some years ago yielded a variety of organisms in the cultures secured by bronchoscopy. The one organism which appeared in almost every culture was the nonhemolytic streptococcus. These findings agree with those reported by Marvin[14] in 1932.

Because these cases are chronic and resist efforts to cure them, the unfortunate victims are too often given inadequate treatment. But even if a cure cannot be obtained their lives can be made easier by proper care.

The first objective is an early diagnosis. A patient with a chronic cough which produces small quantities of sputum should be suspected of having bronchiectasis, especially if the sputum is foul. The cough and sputum are more marked when the patient lies down. Ordinary examination of the lungs may yield nothing more than some sticky râles at the base. Roentgen examination may or may not show the dilated bronchi. Bronchoscopy should be done, especially if there is any evidence of atelectasis. Secretions can be sucked out for culture and an autogenous vaccine can be made if required. If atelectasis is present, the cause of the obstruction can be determined and removed. This may be an unrecognized foreign body, a mucous plug, granulations, or an early carcinoma. After removal of the obstruction the lung distal to it will usually fill with air. If the obstruction has not been present for too long a time the bronchi and lung tissue should return to normal unless a carcinoma is present. Following the bronchoscopy, a lung mapping should be done to outline the bronchi. This will definitely establish whether or not bronchiectasis is present.

The lung mapping is best done after the secretions have been removed by suction through the bronchoscope. The most satisfactory mapping is obtained by passing a rubber catheter through the glottis under the guidance of the laryngeal mirror. This is performed in the fluoroscopy room and with the patient under local anesthesia. After the catheter is in place the lipiodol is injected. By using the fluoroscope, the progress of the oil can be watched and directed where it is wanted by changing the position of the patient.

The majority of patients with bronchiectasis have a suppurative involvement of one or more of the paranasal sinuses. Many men have felt that the sinus infection was primarily responsible for the bronchiectasis. Mullin[15] has shown that the infection can reach the lung either by way of the lymphatics or by direct drainage. Others have claimed that neither infection is primary but that they are merely due to extensive co-existing infection of the respiratory tract. It is certain that they do exist together and that it is necessary to treat all localized centers of infection if the best results are to be secured.

Once the diagnosis of bronchiectasis is established, the sinuses should be examined carefully. Those sinuses found to have a suppurative condition in them should be treated and every effort made to clear up the infection. Radical sinus surgery should be done if more conservative measures fail to produce the desired results. I do not regard a hyperplastic membrane without actual suppuration as a condition requiring radical treatment in these cases. Whether the sinus infection is the primary cause or not, it must cleared up if only to take one more load from the patient's health and thereby improve his general condition.

General measures directed toward building up the patient's resistance and general health should be followed. The diet should be checked to ascertain that there are no important omissions. He should have plenty of vitamins, rest, and fresh air.

Treatment of the lung condition per se must of necessity follow one of two courses: one is directed toward keeping the infected cavities as clean as possible and the other toward eradicating the diseased tissue. The latter course is the one of choice in selected cases because it is the only one which holds forth the certainty of a cure. It should be used only in well-established and not too extensive cases, however. A few years ago the mortality rate for lobectomy was very high. Through steady improvement in the technic, it has been decreasing until now it is not of serious moment. Other surgical procedures such as pneumothorax, oleothorax, phrenicotomy, etc., have been of little value because they have compressed the lung tissue while the dilated bronchi have remained unaffected.

The treatment directed toward keeping the infected cavities as clean as possible must be used in all cases. Those who are to be operated upon can be put in better condition to withstand the operation by a thorough course of treatment first. This treatment consists of two important parts:

Postural drainage should be done by the patient both morning and evening. The patient must be instructed in the proper way to do this or he will not obtain satisfactory results. One of the best methods is to have him lie on his face over the side of the bed with the hips and legs on the bed and the shoulders on the floor. A basin should be available to receive the sputum. He should maintain this position for from 20 to 30 minutes. In some cases this may be sufficient to completely drain the cavities. Usually, however, only a partial cleaning results and this makes the second part of the treatment desirable.

The second part is the bronchoscopic aspiration of the secretions at regular intervals. These intervals may vary from once a week to once a month or longer, depending upon the individual case. Some bronchoscopists advise instilling a few cubic centimeters of sterile solution into the bronchi at times and aspirating it out, thus washing out the cavities. Others feel that such a procedure may tend to spread the infection and therefore they depend upon aspiration alone. Following a good cleaning out of this sort the patient may be almost sputum-free for a few days. His general health improves, his appetite increases, and there is a decrease in the odor of the secretions.

Various antiseptics have been employed but I have yet to find one that I felt contributed anything to the treatment. If it is strong enough

to really affect the bacteria it is too strong for the normal mucous membranes. If it is mild enough that it does not damage the normal mucosa it is useless as a sterilizing agent.

Figures 1 and 2 show the progress of a far-advanced case of bronchiectasis. When this patient was first seen she was about eleven years old and her body was merely skin and bones. The roentgen examination showed suppuration in the lung throughout the entire right side. It was

FIGURE 1: Roentgenogram showing extensive involvement of the lung on the right side.

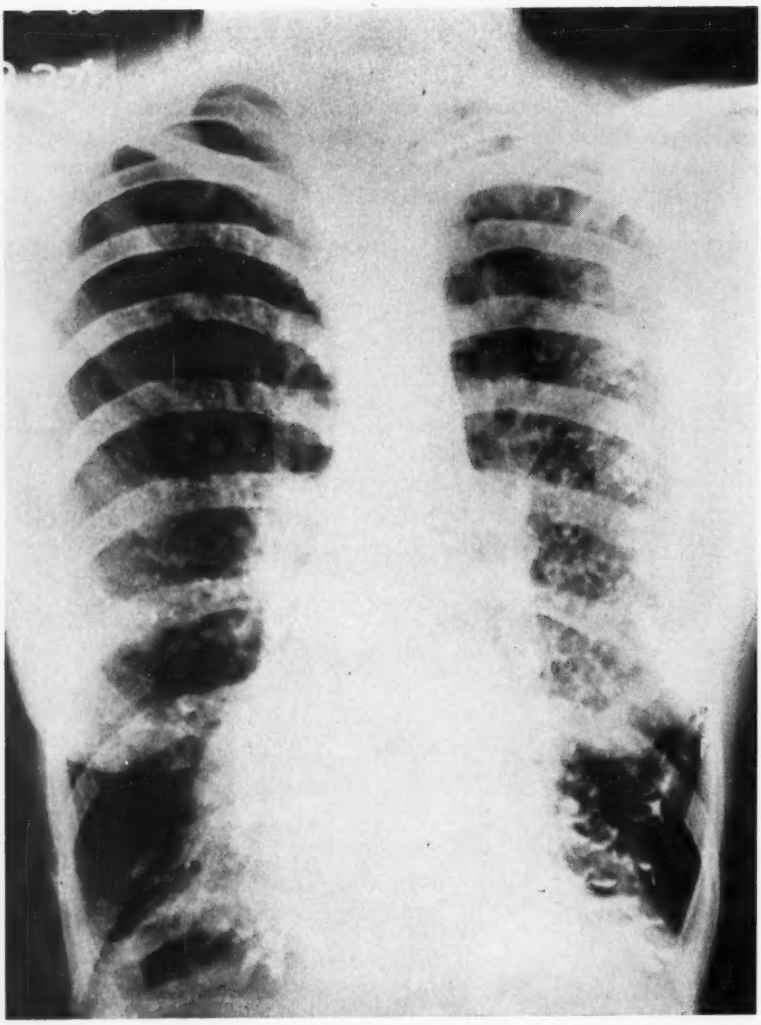

FIGURE 2: Following bronchoscopy, the right lung is clear except for bronchiectasis.

felt that chest surgery would be necessary to drain this extensive suppurative process but that she was in too poor condition to withstand any operation at that time. She was referred to the nose and throat department for bronchoscopic treatments preparatory for operation. This produced such marked improvement that it was decided to continue with her treatments rather than operate at that time.

After the chest had cleared sufficiently the lungs were mapped and the bronchiectasis was found to be so extensive that surgical removal was impossible. However, she has continued her postural drainage and bronchoscopic treatments and is now a buxom, healthy young lady with plenty of vigor and strength although she still raises large quantities of pus every day.

It is interesting to watch the progress of patients who are taking bronchoscopic treatments at regular intervals. For the first or second time they are rather apprehensive and will not relax in spite of morphine and nembutal administered preoperatively. The throat is thoroughly anesthetized with a spray of 2 per cent pontocaine solution followed by direct applications. After a few treatments these patients learn that the more relaxed they are the easier is the procedure. Later they usually voluntarily ask that the sedatives be eliminated and many even ask to have the local anesthetic omitted. They have learned how to cooperate and do not mind the manipulations but they do object to the grogginess which results from the sedatives and the numbness from the anesthesia.

The allergic aspects of bronchiectasis are well worth further investigation. If such a basis is established, it will give us an additional and very valuable weapon with which to combat this condition.

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THE IMPORTANCE OF THE ROENTGEN EXAMINATION IN THE DIAGNOSIS OF REGIONAL ILEITIS

Report of a Case

JOSEPH C. ROOT, M. D.

Regional ileitis is a condition of unknown etiology which has been recognized for many years, although it did not receive the attention it deserved until the report of Crohn et al in 1932[1]. At that time they reported a series of cases to which they applied the term regional ileitis, since the condition was thought to be a disease entity involving only the terminal segment of the ileum. Since that time, however, cases have been seen in which not only the terminal ileum but other parts of the small bowel, as well as the cecum were involved. Indeed, it is not uncommon for several segments of the small intestine to show the changes typical of this disease with areas of normal bowel intervening. The term used to describe this condition is, therefore, not entirely satisfactory, a better and more descriptive term such as nonspecific granulomata of the intestine being preferable. It is doubtful, however, whether this will supersede the original appellation, since it has come to have a definite meaning.

Regional ileitis, while not common, occurs frequently enough that one should think of it when a patient complains of symptoms in the lower right abdominal quadrant. This is especially true in a young adult male because the greatest incidence occurs in this sex at this age period. The following case presents a rather typical picture of the disease and emphasizes the value of the roentgen examination in establishing the diagnosis.

The patient, a young man 26 years of age, presented himself with the complaint of "tenderness of the intestines" and attacks of diarrhea. He stated that he was perfectly well until one and one-half years previous to our examination when he had mild attacks of diarrhea consisting of three or four loose stools a day. Since that time he had had no distress nor had there been any blood or mucus in the stools. The diarrhea persisted for several months, then he had a spontaneous recovery and felt quite well. About five months previously, he experienced rather sharp pains across the abdomen and in the region of the umbilicus. There was no relationship between the pains and the taking of food. No relief was obtained by taking soda, but milk gave relief for a few seconds. At this time the patient first consulted a physician and he ordered a roentgen examination of the colon. No organic lesion could be demonstrated at that time but the administration of the enema reproduced at least a part of the abdominal distress, and relief was obtained upon expulsion of the enema. A bland diet was prescribed and this gave partial relief from the symptoms. A few

weeks before admission there had been a recurrence of the pain and at this time it was more severe in character and was accompanied by three or four loose, watery stools each day.

At the time of examination at the Clinic, the patient said he felt exhausted and tired, and constantly had a feeling of distress in the epigastrium. Recently, enemas had been the only means of relief and these were effective for only a very short time. During this period of illness there had been a gradual loss of 18 pounds in weight.

The family history and past history were essentially negative. Both father and mother were living and well except that the father had "stomach trouble." There had been no operations except a tonsillectomy in 1926, and he had had no serious injuries or disease. The general health had been quite good until the onset of the present illness, one and one-half years before, and the patient had been able to follow his vocation as salesman.

Physical examination, except for the abdomen, revealed normal findings for a young, white male. The abdomen was soft with no localized or general rigidity or spasm. There was, however, definite tenderness which could be elicited by moderate pressure over the right quadrant; this was more marked over the outer aspect. No definite mass could be palpated at this time. A digital examination of the rectum disclosed a tender mass in the right lower quadrant of the abdomen. The clinical impression was an appendiceal abscess.

Proctoscopic examination showed an edematous area five inches from the anus. At this point, pus appeared from the wall of the bowel and an abscess cavity was palpated bimanually.

Laboratory findings: The urine was normal except for a trace of albumin on one occasion. Examination of the feces on admission showed a greenish liquid stool containing ++ pus and +++ mucus. No occult or gross blood could be demonstrated and the examination was negative for ameba and ova.

The level of the urea was 33 mg. and of blood sugar, 79 mg. per 100 cc. at the time of the original examination. The blood Wassermann and Kahn tests gave negative reactions. Examination of the blood at the time of admission showed 5,100,000 red blood cells, 14,600 white blood cells, and 82 per cent hemoglobin. The differential blood count showed 83 per cent polymorphonuclear neutrophils, 6 per cent lymphocytes, 9 per cent monocytes, and 2 per cent polymorphonuclear eosinophils. The red blood cells showed moderate central pallor, moderate anisocytosis, and slight poikilocytosis.

Roentgen examination: At the time of admission, only the colon was examined. The report of this examination was: "terminal ileitis

with fistula and abscess." The colon was seen to be normal except for evidence of compression on the right side of the sigmoid just proximal to the rectosigmoid junction (Fig. 1). The terminal ileum was narrowed and showed abnormal mucosal markings. A fistulous tract led toward the midline from a point about four inches proximal to the ileocecal valve (Fig. 2). Tenderness was elicited in this region by moderate pressure during the fluoroscopic examination.

FIGURE 1: Roentgenogram made in an oblique position immediately after filling the colon with barium. Small, rounded defect on the right side of the sigmoid produced by pressure of the abscess. Small segment of the narrow terminal ileum is visualized.

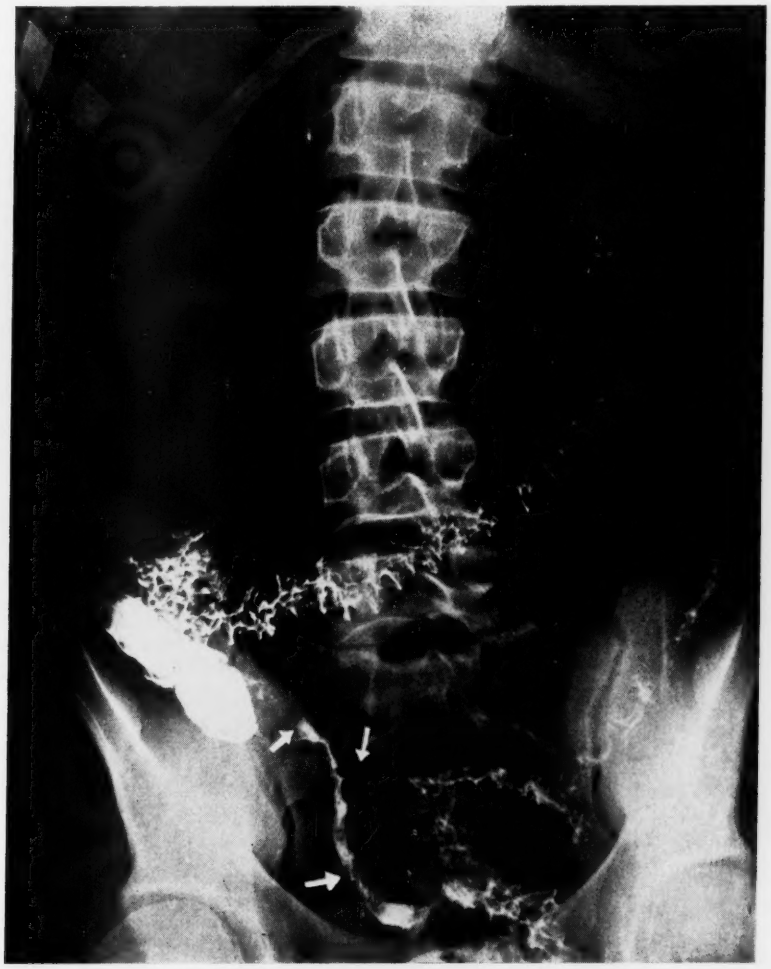

FIGURE 2: Roentgenogram made after expulsion of the barium enema. The terminal ileum is seen to be definitely narrowed. The mucosal pattern is altered and there appear to be present small filling defects resembling polypoid projections. A small fistulous tract is visualized, evidently leading into the abscess cavity.

Operation: An exploratory laparotomy and ileocolostomy were performed under spinal anesthesia. A small amount of slightly blood-tinged, free peritoneal fluid was seen to be present upon opening the peritoneal cavity. Inspection of the terminal ileum revealed the typical changes of a regional ileitis. The terminal ileum was considerably thickened and indurated with rather marked injection of the serosal

surface and some grayish exudate. The exact extent of the involvement could not be determined because of adhesions. The inflammatory mass extended toward the left side of the pelvis in the region of the sigmoid which had previously been demonstrated by the roentgen examination. The cecum in proximity to the terminal ileum showed a small amount of involvement with slight induration and injection of the serosal vessels. The appendix was also present in the inflammatory mass and was definitely enlarged. The ascending colon distal to the cecum was entirely free from any involvement. An anastomosis was made between the small bowel, at a point about eighteen inches proximal to the involved area, and the transverse colon, just proximal to the hepatic flexure. A catheter was inserted into the ileum about six inches proximal to the ileocolostomy.

The convalescence was uneventful, the ileostomy tube was removed on the eighth postoperative day, and the wound was well healed at the time of discharge from the hospital. Resection will be done later.

This case reveals several features which have been present in other cases of the same disease and which merit consideration. In reviewing the symptom complex of regional ileitis, it must be admitted that there are no pathognomonic signs or symptoms. The symptom, however, which is most commonly present is diarrhea, such as was mentioned in the case reported here. This may be moderate in character and either constant or remittent in type. In most of our cases pus and mucus have been found in the stools although this is not always the rule. Pain, if present, is generally of a rather indefinite type, generally being described as dull or cramp-like in character; it will usually be on the right side or around the umbilicus. The pain may not be very marked until late in the disease; it is remarkable to see the amount of involvement which may be present in the intestine while the patient has so few subjective symptoms. Later in the course of the disease there will be loss of weight, anemia, and exhaustion. In many cases the disease goes on to formation of an abscess or fistula. The course of the disease is not limited and may vary from a few months to a couple of years. Patients may be operated upon for appendicitis without the lesion being recognized as due to regional ileitis. The usual course in such a case will be the development of a fecal fistula which tends to become chronic and refuses to close.

The pathological picture is characterized by varying degrees of fibrosis involving all the layers of the bowel. There is, of course, quite a difference in the appearance of the intestine, depending upon the stage of the disease and the severity of the involvement.

Usually, a rather marked mesenteric lymphadenitis is present. The diameter of the involved segment is diminished and there is a general

stiffness of the walls due to the infiltration. In the more advanced and less acute cases there will be formation of cicatricial tissue which, in turn, causes obstruction at that point. In the more acute cases the exterior of the bowel shows a marked redness and injection of the serosal blood vessels, as well as a roughened granular appearance of the serosa. On the mucosal surface are serpiginous ulcerations extending along the mesenteric border, and these are covered with a grayish membrane. Between the ulcers are islands of swollen mucosa which may give the appearance of polypoid lesions.

The condition, from the clinical standpoint, must be differentiated from appendicitis, tuberculosis of the intestine, chronic nonspecific ulcerative colitis, and the deficiency states. A positive diagnosis is made by the roentgen examination. Preferably, this should include the administration of the barium meal and the making of progress films of the passage of the opaque meal through the intestinal tract. The signs of this disease as revealed by the roentgen examination are narrowing of the lumen or the so-called "string sign," which gives rise to obstruction of varying degrees and generally some dilatation of the bowel proximal thereto. The mucosal pattern of the involved segment is usually altered and may even appear to have filling defects or polypoid formations. The motility films, as mentioned previously, are very important and often the film made six hours after the ingestion of the barium meal will give the most information. The roentgen examination of the colon may or may not give much information, depending upon how much of the opaque solution flows through the ileocecal valve. In some cases no barium will get through and the examiner will have no clue as to the real nature of the disease process. Fortunately, some barium generally passes into the small bowel and visualization of a portion, at least, of the terminal ileum is possible. In some instances the involved part of the bowel may be very irritable and it will not be possible to fill it completely, due to the rapid emptying. From the viewpoint of the roentgenologist the chief differentiation must be made from tuberculous enteritis but this is not always possible, even the surgeon and pathologist having difficulty in doing this at times. Of course if the patient has pulmonary tuberculosis, the probability will be that the intestinal lesion will be of the same etiology. From the roentgen appearance alone, the chief reliance must be placed upon the pathological process as it appears during the course of the examination. Regional ileitis, as a rule, will be confined to the small bowel alone, whereas the tuberculous infection will show an affinity for the region of the ileocecal valve, involving the cecum as well as the ileum. In those cases of regional ileitis which do involve the cecum and those of tuberculous enteritis

with negative chest findings, the correct diagnosis may not be made until the specimen is examined and reported upon by the pathologist.

Summary

Regional ileitis is a not uncommon disease which occurs in young adults with a much higher incidence in males.

Symptoms indicating the presence of this condition are: unexplained diarrhea, indefinite pain and tenderness in the right lower quadrant of the abdomen, and a mass in the appendiceal region.

The diagnosis is best made by means of the roentgen examination. The most important part of this examination is observation of the passage of the opaque meal through the small intestines. The film made six to nine hours after the ingestion of the barium will be most apt to reveal the true nature of the lesion.

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TUMORS OF THE RENAL PELVIS

Report of a Case

F. C. SCHLUMBERGER, M. D.

Tumors of the renal pelvis, by reason of their infrequent occurrence and diagnostic complexity, have a special significance not entirely characteristic of other types of renal tumors. These growths are comparatively uncommon and it is generally considered that they comprise from 5 to 7 per cent of all renal tumors. In a series of 341 renal tumors seen at the Cleveland Clinic, 13 or 4.2 per cent were or had their origin in the renal pelvis. It is of interest to note that no such tumor was recorded in this Clinic between January, 1933, and December, 1938. In December, 1938, two cases were seen, one of which is here reported.

REPORT OF CASE

History: The patient was a man, 54 years of age, whose occupation for twenty years had been that of a laborer in a stone quarry. He came to the Clinic on December 14, 1938. His chief complaint was of bloody urine, which had been present for about two months. He had always enjoyed good health with the exception of a chronic cough and shortness of breath. The cough had never been productive. Associated with the hematuria, mild dysuria and occasional nocturia developed. The urine was diffusely red at all times and was not clear on any occasion following the onset of hematuria. He fatigued quite easily and had lost about ten pounds in weight.

The past history was non-revealing. He was a Polish immigrant and contacts with his family had been severed at an early age.

Physical Examination: The patient was a fairly well nourished, well developed man; his temperature was normal; the pulse rate was 72 beats per minute and the blood pressure was 130 systolic and 90 diastolic. He was rather pale but there were no signs of severe, long-standing bleeding.

Examination of the head and neck indicated only improper dental attention. There were no enlarged cervical glands. The chest was somewhat emphysematous with diminished excursion on both sides. There were fine, rather dry râles over the entire lung fields. The heart was not enlarged and its function was good. There were no audible murmurs. The abdomen was not tender and no masses were present. Although there was some tenderness over the right costovertebral area on deep percussion, one could not demonstrate any mass in this region. No tenderness was elicited on the left side and there were no masses present. The genitalia were normal. On digital examination, the prostate was found to be mildly enlarged and benign in character. No varicose veins

were present in the lower extremities and all reflexes showed normal response.

Laboratory Data: The specific gravity of the urine was 1.020, the reaction of the urine was alkaline; there was one plus albumin but no sugar. Microscopically, the specimen was heavily loaded with red blood cells and some pus cells. Complete examination of the blood showed 3,950,000 red blood cells, 68 per cent hemoglobin, and 9,100 white blood cells. Of these, 55 per cent were polymorphonuclear neutrophils, 40 per cent lymphocytes, and 5 per cent monocytes. The value of the sugar determination was 97 mg. and of the urea 54 mg. per 100 cc. of blood. The sedimentation rate was 0.4 mm. and the Wassermann and Kahn tests gave negative reactions.

Roentgen examination of the chest showed a definite silicosis with some evidence of a superimposed tuberculosis in the upper portion of the left lung. Repeated examinations of the sputum were negative for tubercle bacilli and follow-up roentgenograms of the chest also disproved the presence of tuberculosis. Roentgen examination (plain plate) of the kidneys, ureters, and bladder showed normal kidney outline and no suspicious urinary tract shadows; there was a marked osteoarthritis of the spine.

Cystoscopic Examination: The cystoscope was introduced without difficulty and there were about 25 cc. of bloody urine in the bladder. Upon irrigating the bladder it was noted that the return solution cleared readily, suggesting that the bleeding probably was coming from above the bladder. Thorough examination revealed no pathology in the bladder but each efflux of urine from the right ureteral orifice was definitely bloody. Catheters were passed to both kidney pelves without meeting any obstruction. There was an immediate flow of urine from both catheters. That from the right was very bloody and that from the left was clear. Five cc. of indigo carmine were injected intravenously and made its appearance from the left catheter in 4 minutes and from the right in 5 minutes, both in good concentration.

A bilateral pyelogram was made after injecting 8 cc. of solution into each kidney pelvis. The left pyelogram showed a normal kidney. The right (Fig. 1), however, showed a filling defect in the pelvis due either to blood clots or possibly a tumor of the kidney pelvis.

The patient was placed on complete bed rest for six days, at the end of which time the cystoscopic examination was repeated and a right ureteropyelogram was made which showed the same filling defect in the pelvis which was interpreted as probable tumor of the renal pelvis (Fig. 2). The ureter appeared normal and without filling defects.

On December 29, 1938, a right nephrectomy was performed under spinal anesthesia. The kidney was readily exposed and a small mass

FIGURE 1: Retrograde pyelogram showing a punched-out filling defect, with slightly moth-eaten edges at the ureteropelvic junction of the right kidney, probably a tumor. Overlying this shadow was a larger, less dense filling defect, the edges of which were smoother. This was interpreted as a blood clot.

FIGURE 2: Recheck retrograde pyeloureterogram showing the same filling defect and a normal ureter. The final interpretation was tumor at the ureteropelvic junction of the right kidney pelvis.

in the pelvis could be felt on gentle palpation. The ureter was exposed and appeared entirely normal. It was severed as close to the bladder as possible through the kidney incision. The remainder of the procedure was without incident.

The postoperative convalescence was quite uneventful although some difficulty was encountered because of the silicosis demonstrated in the

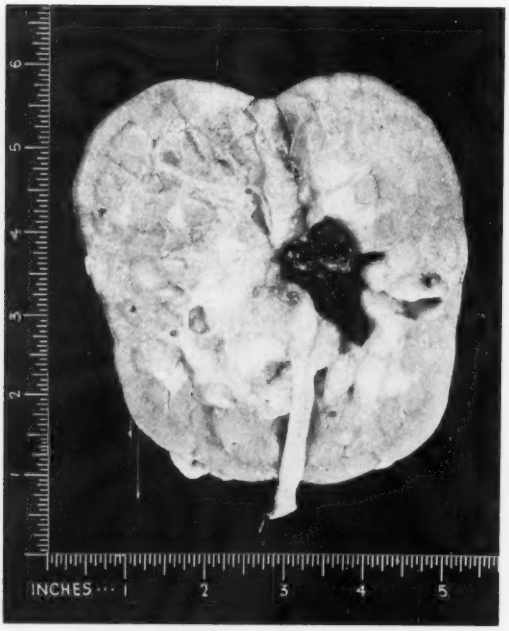

FIGURE 3: Photograph of gross specimen.

chest. The patient was discharged from the hospital on the eighteenth postoperative day.

Pathological Examination: Grossly, the specimen consisted of a fairly normal appearing right kidney and major portion of the right ureter. Gross examination of the sectioned kidney revealed a mildly dilated pelvis filled with a large blood clot. On removing the clot one saw a soft, flat tumor mass, measuring 3 x 2.5 cm. (Fig. 3). This was just at the ureteropelvic junction and extended up into the pelvis. The medullary and cortical tissue otherwise appeared normal. The ureter appeared to be entirely normal with no evidence of implanted tumor tissue.

Histologic examination of sections through the tumor showed a carcinoma arising in the pelvic mucosa and infiltrating the adjacent stroma (Fig. 4).

Diagnosis: Papillary type of carcinoma of the kidney pelvis without evidence of metastasis.

DISCUSSION

Thirteen cases of tumors of the kidney pelvis have been recorded at the Cleveland Clinic. They include papillomas, squamous cell

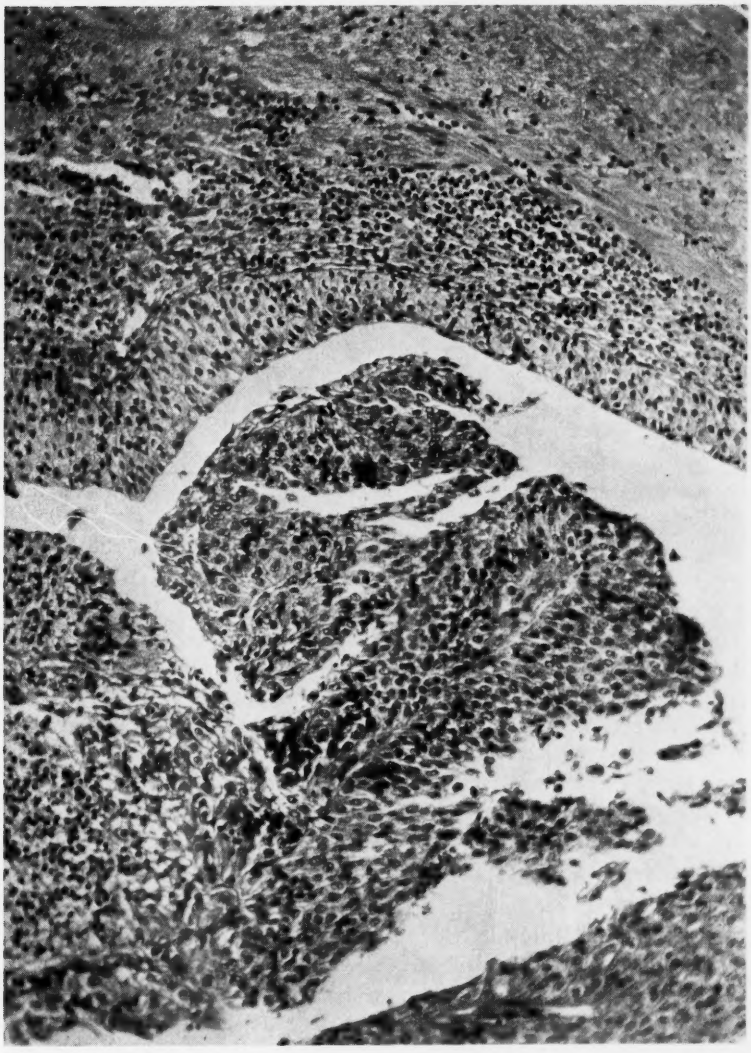

FIGURE 4: Photomicrograph of section through tumor.

carcinoma, and papillary carcinomas. The average age of the patients in this group was 57 years. Twelve tumors occurred in males while only one was found in a female. The side most commonly involved was the left, nine occurring on this side and four on the right.

Symptomatology and Physical Findings: The symptomatology of this group of tumors is similar to that of renal tumors as a whole with

perhaps one or two exceptions. In this group of thirteen patients, hematuria was the only complaint in eight cases, hematuria and pain in four, and frequency was the only complaint in one case. Hematuria, of course, is perhaps the most important symptom in any kidney tumor, but is characterized in tumors of the kidney pelvis by the fact that it often is the only complaint. The bleeding may be painless and this is particularly true in papillary tumors of the kidney pelvis which bleed easily because of the vascularity of the tumor in contrast to the squamous cell type which is relatively avascular.

Pain rarely accompanies hematuria in these cases because, as a rule, the tumor is not large and the kidney is not palpable on physical examination. When pain does occur it is often the result of pelvic block with resulting pyelectasis. In the four cases in which hematuria was accompanied by pain, it was of interest to note that the kidney had enlarged to such proportions that it was definitely palpable. In contrast there is that group of kidney tumors comprised by hypernephromas, Wilms' tumors, and adenocarcinomas, in which one often finds that although hematuria may be present the patient may tell you of a mass which usually is associated with pain. These tumors are also, as a rule, accompanied by extreme loss in weight which is not characteristic of renal pelvic tumors.

Diagnosis: The diagnosis of pelvic tumors is made chiefly by urographic study. Although the majority are associated with profuse hematuria, this finding without definite palpable evidence of renal tumor may be deceptive. Urographic evidence of filling defects in the pelvis and ureter may again be deceptive and does not necessarily represent neoplasm. These defects may occur as a result of a clot, a shadowless calculus, or granulomatous or cystic changes along the ureter and renal pelvis.

Thus a true diagnosis can be established only by thoroughly correlating the urographic findings with the clinical history and cystoscopic findings. If the filling defect is consistently present through repeated retrograde pyelograms, if there is no evidence of chronic infection or stone, and observation is made at intervals between bleeding, the evidence is conclusive that such an abnormality is created by a pelvic tumor. Intravenous urography may be of assistance in certain cases but delineation by this means is seldom as clean-cut as by retrograde pyelography.

Cytological study of the urine may be of great value in the accurate diagnosis of neoplasms of the renal pelvis. Microscopic examination of the sediment in the urine may show bits of tissue which contain tumor cells. This is especially true of the papillary tumors. During the course of ureteral catheterization small pieces of tumor tissue which are

adequate for cellular identification of tumor tissue may be obtained in the washings from the renal pelves.

Treatment: The treatment of tumors of the renal pelvis is surgical and varies with the type of tumor encountered. As in all tumors, early diagnosis is essential for the future welfare of the patient. Because the hematuria is often painless, many of these patients are not seen in the early stages of the disease. In the squamous cell type, the growths as a rule have extended beyond hope of cure. Simple nephrectomy in this type is usually all that is necessary as it has little tendency to involve the ureter.

However, in the papillary tumors—benign and malignant—more than nephrectomy is required, although this is the operation which is usually performed first in the majority of instances. Ureterectomy, if not done during the initial procedure, may follow by matter of choice or because of recurrence of the tumor. Ureterectomy should include the intramural portion of the ureter in view of its being the most common point for recurrence or implantation to take place.

Many of these pelvic tumors are not radiosensitive. However, in the light of recent reports on the beneficial effects of radiation on papillary neoplasms of the bladder, it may be deemed advisable to follow this course with kidney tumors. This is entirely dependent upon the findings in each individual case.

Pathology: With few exceptions these tumors are epithelial, the majority being of the papillary variety and very similar to those of the bladder. The papillary tumors constitute about three-fourths of all of the renal pelvic growths. Five of our cases were of the squamous cell type and eight were of the papillary type of varying degrees of malignancy. The truly benign papillomata are apparently of infrequent occurrence. Malignant changes appear to be the rule since many of these tumors remain silent for a long period of time.

The growth may be tall and pedunculated or short and spreading. Multiplicity is common and there may be implantation in the ureter or even the bladder. When the growth is of the flat, spreading type such as the one reported, infiltration is early and a large portion of the kidney may become involved, obliterating its pelvic origin. The cells are usually made up of large, oval, vesicular nuclei, blue-staining cytoplasm, and they have a tendency toward alveolar arrangement. The squamous cell type is usually flat and shows early infiltration with a tendency toward pearl formation. These tumors are often associated with pre-existing factors such as calculi or leukoplakia.

Prognosis: The variable factors in the prognosis of renal neoplasm are notable in that there is a general lack of agreement among numerous

authors and their observations. In the squamous cell type, metastasis is usually widespread when the tumor is found, dissemination through the blood stream being evidenced by lesions in the lungs, liver, and bones. In many cases extension of the local lymphatics has taken place. The true papillary type of tumor offers a ray of hope although local recurrence in the bladder is not uncommon. In our series, five of the thirteen patients died within six months following operation, three of these had had squamous cell carcinoma and two papillary carcinoma. In three of these cases, metastases were demonstrable in the lungs, and in one of the squamous cell types metastasis was generalized. Three patients survived only one year and metastasis to the lungs was demonstrated in one case. One patient survived nephrectomy for epidermoid carcinoma of the kidney pelvis for a period of three years with final metastasis to the lungs and femur. Two patients with papillary carcinoma of the kidney pelvis were alive and well four years after operation. Two cases have been of recent date. We may conclude from this study that the prognosis is very grave where squamous cell carcinoma is proven. In the papillary group of tumors the extensiveness of the growth, the invasiveness and degree of malignancy, and the time of operation largely determine the future outcome of the patient.

THE FRANK E. BUNTS INSTITUTE

Course In

Benign and Malignant Tumors

On

MONDAY, TUESDAY, and WEDNESDAY
APRIL 3, 4, and 5, 1939

The Frank E. Bunts Institute

The Frank E. Bunts Institute will present a course in "Benign and Malignant Tumors," on Monday, Tuesday, and Wednesday, April 3, 4, and 5, 1939.

The program of the course and an application blank will be found on the succeeding pages of this Quarterly.

PROGRAM

BENIGN AND MALIGNANT TUMORS

Monday, April 3rd, 1939

8:30 A. M.— 9:00 A. M.	Registration	
9:00 A. M.	Welcome	
9:00 A. M.—10:00 A. M.	Diagnosis and Treatment of Brain Tumors	W. J. Gardner, M. D.
10:00 A. M.—10:30 A. M.	Tumors of the Orbit	A. D. Ruedemann, M. D.
10:30 A. M.—11:00 A. M.	Benign and Malignant Tumors of the Nose and Sinuses	Paul M. Moore, M. D.
11:00 A. M.—11:30 A. M.	Laryngeal Tumors	Justin M. Waugh, M. D.
11:30 A. M.—12:00 Noon	Tumors of the Jaws	C. A. Resch, D. D. S.
12:00 Noon— 1:00 P. M.	Luncheon	
1:00 P. M.— 1:30 P. M.	Tumors of the Lip and Tongue	Geo. H. Curtis, M. D.
1:30 P. M.— 2:30 P. M.	Tumors of the Neck	R. S. Dinsmore, M. D.
2:30 P. M.— 3:00 P. M.	Mediastinal Growths	B. H. Nichols, M. D.
3:00 P. M.— 3:30 P. M.	Tumors of the Lung	A. C. Ernstene, M. D.
3:30 P. M.— 4:15 P. M.	Benign and Malignant Tumors of the Skin—Pre-cancerous Lesions	E. W. Netherton, M. D.
4:15 P. M.— 5:00 P. M.	Tumors of the Vertebral Column and Spinal Cord	A. T. Bunts, M. D.
6:30 P. M.	Dinner	
8:15 P. M.	Guest Speaker—Subject to be announced	

Tuesday, April 4th, 1939

9:00 A. M.— 9:30 A. M.	Esophageal Lesions—Differential Diagnosis	E. N. Collins, M. D.
9:30 A. M.—10:30 A. M.	The Diagnosis of Early Lesions of the Stomach—Use of the Gastroscope	R. J. F. Renshaw, M. D.
10:30 A. M.—10:45 A. M.	Surgical Management of Early Carcinoma of the Stomach	T. E. Jones, M. D.
10:45 A. M.—11:45 A. M.	Diagnosis of Neoplasms of the Colon	E. N. Collins, M. D.
11:45 A. M.—12:30 P. M.	Roentgen Interpretation of Gastro-Intestinal Lesions	J. C. Root, M. D.
12:30 P. M.— 1:30 P. M.	Luncheon	
1:30 P. M.— 2:30 P. M.	Surgical Treatment of Carcinoma of the Colon and Rectum	T. E. Jones, M. D.
2:30 P. M.— 3:30 P. M.	Malignancy in Relation to Blood Diseases	Russell L. Haden, M. D.
3:30 P. M.— 4:00 P. M.	Bone Tumors—Benign	J. I. Kendrick, M. D.
4:00 P. M.— 4:30 P. M.	Bone Tumors—Malignant	J. A. Dickson, M. D.
4:30 P. M.— 5:00 P. M.	Endocrine Aids in the Diagnosis of Tumors	E. P. McCullagh, M. D.
6:30 P. M.	Dinner	
8:15 P. M.	Questions and Answers Case Reports, Differential Diagnosis Discussion	

Wednesday, April 5th, 1939

9:00 A. M.— 9:30 A. M.	Tumors of the Breast—Diagnosis and Treatment	George Crile, Jr., M. D.
9:30 A. M.—10:30 A. M.	The Treatment of Cancer of the Breast	U. V. Portmann, M. D.
10:30 A. M.—11:30 A. M.	The Criteria of Malignancy	Allen Graham, M. D.
11:30 A. M.—12:00 Noon	Cancerphobia	C. L. Hartsock, M. D.

Wednesday, April 5, 1939—Continued

12:00 Noon—	1:00 P. M.	Luncheon	
1:00 P. M. –	1:30 P. M.	The Biophysical Theory of Cancer	Otto Glasser, Ph. D.
1:30 P. M. –	2:15 P. M.	Tumors of the Kidney	W. E. Lower, M. D.
2:15 P. M.—	3:00 P. M.	Bladder and Ureteral New Growths	W. J. Engel, M. D.
3:00 P. M. –	3:45 P. M.	Tumors of the Testes and Prostate	C. C. Higgins, M. D.
3:45 P. M.—	4:45 P. M.	Cancer of the Cervix and other Growths in the Pelvis	T. E. Jones, M. D.

REGISTRATION BLANK

....., 1939

THE FRANK E. BUNTS INSTITUTE
Cleveland Clinic
Cleveland, Ohio

Gentlemen:

Please register me for the course in "Benign and Malignant Tumors" which is to be given April 3, 4, and 5, 1939.

I am enclosing a check for $5.00 and the remainder of the fee, $5.00, will be paid on registration, April 3.

Name .....

Address .....

.....
Medical School from which Graduated

Note: Checks should be made payable to The Frank E. Bunts Institute and sent to A. D. Ruedemann, M. D., Cleveland Clinic, Cleveland, Ohio.

Exhibits

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DEPARTMENT OF ROENTGENOLOGY

Tumors of the Gastro-Intestinal Tract ..... B. H. NICHOLS, M. D. AND J. C. ROOT, M. D.

Metastatic Lesions ..... B. H. NICHOLS, M. D. AND J. C. ROOT, M. D.

DEPARTMENT OF SURGERY

Tumors of the Breast ..... GEORGE CRILE, JR., M. D.

Tumors of the Rectum ..... THOMAS E. JONES, M. D.

DEPARTMENT OF OPHTHALMOLOGY

Orbital Tumors ..... A. D. RUEDEMANN, M. D. AND R. J. KENNEDY, M. D.

DEPARTMENT OF DERMATOLOGY

Tumors of the Skin ..... E. W. NETHERTON, M. D. AND GEO. H. CURTIS, M. D.

Tumors of the Tongue and Lip ..... E. W. NETHERTON, M. D. AND GEO. H. CURTIS, M. D.

DEPARTMENT OF DENTISTRY

Tumors of the Jaw ..... C. A. RESCH, D. D. S.

DEPARTMENT OF MEDICINE

Tumors of the Esophagus and Stomach ..... E. N. COLLINS, M. D. AND R. J. F. RENSHAW, M. D.

Exhibits

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DEPARTMENT OF NEUROSURGERY

Tumors of the Brain ..... W. J. GARDNER, M. D. AND A. T. BUNTS, M. D.

Tumors of the Vertebral Column and Spinal Cord ..... W. J. GARDNER, M. D. AND A. T. BUNTS, M. D.

DEPARTMENT OF ORTHOPEDICS

Benign and Malignant Bone Tumors ..... J. A. DICKSON, M. D. AND J. I. KENDRICK, M. D.

DEPARTMENT OF GENITO-URINARY DISEASES

Tumors of the Genito-Urinary Tract ..... WILLIAM E. LOWER, M. D., C. C. HIGGINS, M. D., W. J. ENGEL, M. D. AND F. C. SCHLUMBERGER, M. D.

DEPARTMENT OF OTOLARYNGOLOGY

Laryngeal Lesions ..... P. M. MOORE, M. D., J. M. WAUGH, M. D. AND W. L. DEETON, M. D.

Tumors of the Nose and Throat ..... P. M. MOORE, M. D., J. M. WAUGH, M. D. AND W. L. DEETON, M. D.

DEPARTMENT OF ROENTGENOTHERAPY

Classification of Tumors of the Breast ..... U. V. PORTMANN, M. D.

DEPARTMENT OF BIOPHYSICS

The Biophysical Theory of Cancer ..... OTTO GLASSER, PH. D.